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PRINCIPAL INVESTIGATOR: Maha Hussain, MD, FACP, FASCO

CONTRACTING ORGANIZATION:
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14. ABSTRACT

Purpose: The objective of the Prostate Oncology Program at the University of Michigan is to understand the biology of prostate cancer and to use this information to develop new tools for the detection, diagnosis, prevention, treatment and survivorship of prostate cancer.
Scope: The scope is to translate scientific observations on the biology of prostate cancer into therapeutic clinical trials which incorporate correlative measures for assessing response, progression and therapeutic effect.
Major progress. The focus of the University of Michigan during these five years of the DOD-PCCTC has been to maintain and improve the necessary infrastructure to facilitate the execution of multicenter trials; a process that includes data sharing, opening and accruing to Consortium trials, disseminating initial findings from PCCTC-DOD trials to the Consortium and larger research community, as well as introducing important and novel translational clinical trials to the DOD-PCCTC for member participation.
Results. The University of Michigan has introduced ten trials for Consortium participation during the five year period of the 2009 CCA award (4/1/2009-3/31/2014), three of which stem from scientific data generated by our Prostate Cancer scientists. Seven trials were coordinated by the University of Michigan and two of these trials investigated NCI agents. Accrual is completed for fourteen trials and clinical and biological samples analysis is near completion resulting in several abstracts. In the fifth year, a poster was presented at the 2013 ASCO Annual meeting (C11-079, XL184), an abstract at the 2014 ASCO Genitourinary Cancers Symposium (c12-111, PSMA ADC 2301) and three abstracts were accepted for presentation at the Poster Highlights Session Genitourinary (Prostate) Cancers at the 2014 ASCO Annual Meeting (one additional abstract were accepted as publication-only abstract).We have had several manuscripts(published/submitted) during this final fifth year of the funding period. (c09-031, ABT-888 in *Investigational New Drugs* in April 2014 and c09-044, TAK-700, in *Clinical Cancer Research* submitted in May 2014) and Dr. Smith was a co-author on two manuscripts reporting results from the c11-079, XL184 trial and the c10-073, Cediranib/Dasatinib trial.
Significance. Within the cooperative environment of DOD-PCCTC our mission is to develop and test, in a timely manner, novel biologically-based therapies for prostate cancer. Our goals are to delay disease progression, improve survival and enhance quality of life. The success of this undertaking is greatly facilitated and enhanced by the scientific input and the collaborative approach within the DOD -PCCTC.

15. SUBJECT TERMS
prostate cancer, phase I/II, phase II, clinical consortium

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D. **c07-012- Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC). \. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 137).**

E. **c09-024 – A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 170).**

F. **c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 127).**

G. **c11-079 -Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. Poster presentation at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, 2010.**

H. **c11-079- Cabozantinib (XL184) in metastatic castration resisitant prostate cancer (mCRPC): Results from a phase 2 randomized trial. Oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, Genitourinary Cancer Session (Prostate Cancer), 2011.**

Year 3 (01 Apr 2011- 31 Mar 2013)

I. **c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy.\ American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 97).**

J. **c09-031 - Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 224).**

K. **c09-033 - A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial. American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4532). UMICH - co-author.**

L. **c11-079 - Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial.. American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4516).**

M. **c09-044 - Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study.** Abstract and poster presented by Dr. Hussain at the **27th Annual Congress of the European Association of Urology (EAU). Paris, France. 2012 (abstract and poster #124).**

Year 4 (01 Apr 2012- 31 Mar 2013)

N. **c11-079- Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE). American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session, 2012, J Clin Oncol 30:2012 (suppl: abstr 4513).**

O. **c09-044- Safety and activity of the investigational agent orteronel (ortl) without prednisone in men with nonmetastatic castration-resistant prostate cancer (nmCRPC) and rising prostate-specific antigen (PSA): Updated results of a phase II study. American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session, 2012, J Clin Oncol 30:2012 (suppl: abstr 4549).**

P. **c09-044 – A Phase 2 multicenter study of the investigational single agent orteronel (TAK-700) in nonmetastatic castration resisistant prostate cancer (nmCRPC) and rising prostate-specific antigen.** Abstract and poster presented by Susan Moran Arangio at the **28th Annual Congress of the European Association of Urology (EAU). Milan, Italy. 2013 (abstract and poster #100).**

Q. **09-044- Safety, efficacy, and health-related quality of life (HRQoL) of the investigational single agent orteronel (ortl) in nonmetastatic castration-resistant prostate cancer (nmCRPC): Updated results. Poster presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, 2013, J Clin Oncol 31, 2013 (suppl; abstr 5076)**

Year 5 (01 Apr 2013- 31 Mar 2014)

R. **c12-111- A phase II trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC). \ American Society of Clinical Oncology (ASCO) GU Cancers Symposium, 2014, General Poster Session A: Prostate Cancer, J Clin Oncol 32, 2014 (suppl 4; abstr 83).**

S. **c11-089, Concordance of ETS fusion status of matched metastatic castration-resistant prostate cancer and primary prostate cancer: Data from NCI 9012, a randomized ETS fusion-stratified phase II trial.** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5019.**

T. **c12-111- A phase 2 trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC).** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5023**.

U. **c09-057- Primary outcomes of the placebo-controlled phase 2 study PERSEUS (NCT01360840) investigating two dose regimens of abituzumab (DI17E6, EMD 525797) in the treatment of chemotherapy-naive patients (pts) with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC).** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5030**.

V. **Comprehensive molecular profiling of pretreatment metastatic castration resistant prostate cancer (CRPC): Secondary data from NCI 9012, a randomized ETS fusion-stratified phase II trial** Accepted as a publication-only abstract published in conjunction with **the 2014 ASCO Annual Meeting but not presented at the Meeting**, can be found online only. **Abstract No. e16038**.

***PUBLICATIONS*……..**

Year 1 (01 Apr 2009- 31 Mar 2010)

W. c05-009 – Vorinostat in Advanced Prostate Cancer Patients Progressing on Prior Chemotherapy (National Cancer Institute Trial 6862): Trial Results and Interleukin-6 analysis: A study by the Department of Defense Prostate Cancer Clinical Trial Consortium and University of Chicago Phase 2 Consortium. \ *Cancer*. 2009 Dec 1 2009; 115 (23) 5541-9. PMCID: PMC2917101

X. c05-010 – Cilengitide (EMD 121974, NSC 707544) in asymptomatic metastatic castration resistant prostate cancer patients: a randomized phase II trial by the prostate cancer clinical trials consortium. *Invest New Drugs*. 2011 Dec;29(6):1432-40. Epub 2010 Mar 25. PMCID: PMC2917503

Y. c07-009 – Oral enzastaurin in prostate cancer : A two cohort phase II trial in patients with PSA progression in the non-metastatic castrate state and following docetaxel-based therapy. *Invest New Drugs*. 2011 Dec;29(6):1441-8. Epub 2010 Arp 6. PMID: 20369375

Z. c05-008 - Phase I Study of Ixabepilone, Mitoxantrone, and Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Therapy: A Study of the Department of Defense Prostate Cancer Clinical Trials Consortium.. *Journal of Clinical Oncology* Jun 2009: 2772–2778. PMCID: PMC2698016

Year 2 (01 Apr 2010- 31 Mar 2011)

AA. c05-007 - Phase II study of Cilengitide (EMD 121974, NSC 707544) in patients with non-metastatic castration resistant prostate cancer, NCI-6735. A study by the DOD/PCF prostate cancer clinical trials consortium; *Invest New Drugs.* 2012 Apr;30(2):749-57. Epub 2010 Nov 4. PMCID: PMC3175265

BB. c05-008 – Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy. A Phase 2 Study of the Department of Defense Prostate Clinical Trials Consortium. Cancer. 2011 Jun 1;117(11):2419-25, Epub, 2010 Dec 29. PMID: 21192058

Year 3 (01 Apr 2011- 31 Mar 2012)

CC. c09-024 - A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: a University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study.. Prostate Cancer and Prostatic Diseases (2012) 15, 87–92. PMID: 22006050

Year 4 (01 Apr 2012- 31 Mar 2013)

DD. c11-079- Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. J Clin Oncol Vol 31 No 4 Feb 1 2013, 412-419. PMID: 23169517

EE. c09-033- Repurposing Itraconazole as a Treatment for Advanced Prostate Cancer: A Noncomparative Randomized Phase II Trial in Men With Metastatic Castration-Resistant Prostate Cancer. The Oncologist 2013; 18:163-173. PMCID: PMC3579600

FF. c09-031-Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer. *Invest New Drugs,* 26 April 2014 [Epub ahead of print]. PMID: 24764124

c09-044- Phase II Study of Single Agent Orteronel (TAK-700) in Patients with Nonmetastatic Castration-Resistant Prostate Cancer and Rising Prostate-Specific Antigen. Submitted to ***Clinical Cancer Research***, 05 May 2014, awaiting final decision.

GG. c11-079, Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. ***European Urology*, Epub ahead of print, 20Feb2014. PMID: 24631409**

HH. c10-073, A randomized phase II study of cediranib alone versus cediranib in combination with dasatinib in docetaxel resistant, castration resistant prostate cancer patients. ***Invest New Drugs*, Epub ahead of print, 03May2014. PMID: 24788563**

INTRODUCTION
University of Michigan Comprehensive Cancer Center

The University of Michigan Prostate Oncology Program is an interdisciplinary group of 36 laboratory, translational and clinical researchers from 13 departments and four schools with over $17.8 million in annual direct research support. The Prostate Oncology Program continues its primary mission of translating basic and clinical discoveries in prostate cancer into effective medical solutions. The program includes a Prostate SPORE, a PO1 on the Biology of Prostate Cancer Bone Metastasis, a Department of Defense funded Prostate Cancer Clinical Trials Consortium site (DOD-PCCTC), a prostate-focused Early Disease Research Network (EDRN) site, a NIDDK training grant in Clinical and Translational Research Training in Urology (T32), one PCF Challenge Award and a N01 contract with CTEP (University of Chicago – Early Therapeutics Development with Phase II emphasis group). The Prostate Oncology Program co-led by Drs. Maha Hussain and Evan Keller was ranked "Exceptional" by the NCI scientific reviewers as part of our Comprehensive Cancer Center NCI core grant renewal. The Program is committed to creating and sustaining a multidisciplinary environment for basic and clinical researchers studying prostate cancer. The success of this synergistic approach is reflected in the number of intra- and inter-programmatic publications published by the group in the last five years (the program has over 900 publications, of which 125 publications are in high impact journals (Impact factor >8). It as also been recognized though the leadership of the Prostate Cancer Dream Team through Stand Up to Cancer (SU2C). The objective of the Prostate Oncology Program is to understand the biology of prostate cancer and to use this information to develop new tools for the detection, diagnosis, prevention, and treatment of prostate cancer. This objective is being pursued through investigations addressing four over-arching aims: Aim 1: To investigate the genetic and epigenetic events that contribute to malignant transformation. Aim 2: To characterize aberrations in cellular biology and function in urological cancers. Aim 3: To translate basic scientific discoveries to develop new biomarkers and therapies in urological cancers. Aim 4: To evaluate clinical outcomes with the purpose of guiding therapy development while reducing cancer-related mortality as well as cancer and therapy-associated morbidities. The goals of the Prostate Oncology Program at the University of Michigan are perfectly aligned with those of the Department of Defense's: to combine the efforts of the nation's leading investigators and scientists to test novel therapeutic interventions that will ultimately decrease the overall impact of the disease. That is, to prevent, to detect, and to cure prostate cancer and to improve the quality of life for individuals living with prostate cancer and their families.

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FINAL REPORT — BODY

University of Michigan Comprehensive Cancer Center

The contributions and participation of the University of Michigan as a clinical consortium research site during the entire award period (04-01-2009 to 03-31-2014) of the DOD-PCCTC award are summarized in this report. The focus of the University of Michigan during the period of DOD-PCCTC funding has been to continue work with the consortium investigators and outside sponsors, including the NCI, to bring novel research to the DOD-PCCTC, to continue to actively accrue to DOD-PCCTC trials, and to expand collaboration with other non-consortium institutions.

Fourteen trials have been completed at the end of this fifth year of funding and are undergoing final analysis of clinical and biological samples. These trials and their closure dates are listed below.
c07-012, AT-101, closed 9/14/10, terminated 12/13/11
c08-009, Nab-docetaxel, closed 10/20/09, re-opened 12/1/0/10, closed 1/31/11, terminated 1/8/14
c09-024, Pazopanib, closed 4/20/10, terminated 3/30/11
c09-031, ABT-888, closed 10/22/10, terminated 12/13/11
c09-033, Itraconazole, closed 10/1/10, terminated 11/21/13
c09-044, TAK-700, closed 6/1/7/11, terminated 2/19/13
c11-079, XL-184 RDT, closed to accrual 2/29/12
c09-057, EMD Serono 525797, closed to accrual 10/23/12
c10-072, ARN-509, closed to accrual 5/21/12
c10-073, Cediranib/Dasatinib, closed to accrual 7/31/12 (permanently closed 12/31/12)
c12-111, PSMA ADC , closed to accrual 1/23/14
c12-104, BIND-014, sponsor held enrollment 11/6/13
c11-080, Everolimus +Hormones and Radiation, closed to accrual 4/3/14
c10-071, Tesetaxel - closed as of 8/3/12 due to the sponsor (Genta) declaring bankruptcy and going into receivership during this reporting period.

Another trial (c12-106- TAK-700, C21013) closed to accrual on 1/15/2013 after we received IRB approval of the study on 1/11/2013.
Several abstracts were presented at national meetings from the completed trials **(referenced in the Bibliography).** We continue to maintain and optimize the necessary infrastructure to facilitate the execution of multicenter trials; a process that includes data sharing, opening and accruing to consortium trials, disseminating initial findings from PCCTC-DOD trials to the Consortium and larger research community, as well as introducing important and novel translational clinical trials to the DOD-PCCTC for member participation. Going forward, we will continue to introduce new concepts based on data generated by our scientists taking advantage of the DOD-PCCTC strengths both from an intellectual scientific perspective and accrual abilities, participate in consortium studies and complete analysis and reporting of the University of Michigan-led completed trials.

Administrative Infrastructure

The investigators and research personnel that are funded, in part, by the Department of Defense grant can be found in Table 1. Currently they include four medical oncologists, two radiologists, two pathologists, one data manager, one biostatistician, one clinical research nurses, one study coordinator, one study administrator and one financial specialist.

Table 1. University of Michigan Personnel

Maha Hussain, M.D, FACP, FASCO, Professor, Departments of Internal Medicine and Urology	University of Michigan Comprehensive Cancer Center Internal Medicine, Hematology Oncology 7314 Cancer Center, SPC 5946 Ann Arbor, MI 48109-5946 mahahuss@umich.edu
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Kathleen Cooney, M.D, Professor, Departments of Internal Medicine and Urology	University of Michigan Comprehensive Cancer Center Internal Medicine, Hematology Oncology 7216 Cancer Center, SPC 5948 Ann Arbor, MI 48109-5948 kcooney@umich.edu
Kenneth J. Pienta, MD, Professor, Departments of Internal Medicine and Urology (effective until 12/31/12)	University of Michigan Comprehensive Cancer Center Internal Medicine, Hematology Oncology 7308 Cancer Center, SPC 5946 Ann Arbor, MI 48109-5946 kpienta@umich.edu
Ajjai Alva, M.D. Assistant Professor, Departments of Internal Medicine and Urology (start date 2/1/12)	University of Michigan Comprehensive Cancer Center Internal Medicine, Hematology Oncology C351 Med Inn, SPC5848 University of Michigan Ann Arbor, MI 48109 ajjai@umich.edu
Mahmoud M Al-Hawary, MD, Assistant Professor of Radiology (effective until 1/31/13)	University of Michigan Department of Radiology UH B1-D502F Ann Arbor, MI 48109-5030 alhawary@umich.edu
Matthew S. Davenport, MD, Assistant Professor of Radiology (start date 2/1/13)	University of Michigan Department of Radiology 1500 E. Medical Center Drive, B1 G505 Ann Arbor, MI 48109-5030 matdaven@umich.edu
Stephanie Daignault, MS, Biostatistician, Biostatistics Core	University of Michigan Comprehensive Cancer Center NI8D11 300 NIB SPC 5473 Ann Arbor, MI 48109-5473

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Gregory Campbell, Research Project Administrator	University of Michigan Comprehensive Cancer Center Internal Medicine, Hematology Oncology 7303 Cancer Center, SPC 5946 Ann Arbor, MI 48109-5946 gwcampbe@umich.edu
Mathew Innes, IT Supervisor	University of Michigan North Campus Research Complex Clinical Trials Office 2800 Plymouth Road, Building 300 Ann Arbor, MI 48109-2800 innesm@umich.edu
Cindy Rekowski, Solid Tumor, Team Leader	University of Michigan North Campus Research Complex Clinical Trials Office 2800 Plymouth Road, Building 300 Ann Arbor, MI 48109-2800 crekowsk@umich.edu
Patricia Jo Harvey, GU Data Manager	University of Michigan North Campus Research Complex Clinical Trials Office 2800 Plymouth Road, Building 300 Ann Arbor, MI 48109-2800 harveypj@umich.edu
Morand Piert, M.D., Associate Professor of Radiology (start date 5/1/13)	University of Michigan Department of Radiology 1500 E. Medical Center Drive, B1 G505 Ann Arbor, MI 48109-5028 mpiert@umich.edu
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Rohit Mehra, M.D., Assistant Professor of Pathology (start date 8/1/13)	University of Michigan Department of Pathology 1500 E. Medical Center Drive, 2G 332 Ann Arbor, MI 48109-5054 mrohit@umich.edu
Susan Hansen, Hemotolgy/Oncology Financial Specialist,Senior (start date 4/1/11)	University of Michigan Internal Medicine-Hematology/Oncology Dominos Farms, Lobby J Suite #1200 Ann Arbor, Michigan 48106 shansen@umich.edu

A list of personnel who received any pay for the research efforts described in this report appears in the Supporting Data (**Table F**).

As a consortium research site, the University of Michigan fulfilled the following tasks:

Task #1: Conduct the clinical trials along the lines of research outlined in the proposal. Patient accrual and sample collection (Months 1-48).

Includes patient accrual and biological samples collection for: 1. Studies that have been activated in the final quarter of the previous funding period and 2. All new studies that will be proposed for this funding period. This is for studies initiated both by the University of Michigan and other consortium sites. Outlined in the initial proposal were three research objectives relating to this first task in the Statement of Work.

Objective #1: Exploit biological observations from different states of advanced prostate cancer to develop more effective systemic therapies. This is accomplished through specific areas of focus:

- Targeting pathways of tumorigenesis.
  - Signal transduction
  - Cytotoxic therapy
- Targeting prostate cancer – bone microenvironment metastasis biology.
- Targeting angiogenesis in tumor development and progression.

Objective #2: To develop treatment and tumor specific determinants of response and progression. This is accomplished by carefully selected correlative studies utilizing patient biologic samples and novel imaging techniques.

Objective #3: Continue ongoing collaborative efforts with other institutions performing clinical trials in prostate cancer including the DOD-PCCTC, SPORE clinical trials group, PCF-Therapy consortium, the University of Chicago CTEP Phase II consortium, in addition to other institutions and cooperative groups (RTOG, SWOG). Our objectives are to provide access for a larger group of prostate cancer patients to novel therapies, particularly minority patients and to synergize efforts and resources between different federal and non-federal funding sources.

Table 2 presents all the DOD-PCCTC trials that are either open for accrual or are in the process of being activated for accrual at the University of Michigan. Each trial's specific area of focus as related to Objective #1 can be found in the first column of Table 2. From this table, it is apparent that the University of Michigan is successfully working towards accomplishing Objective 1, carrying out a wide range of clinical trials to develop more effective systemic therapies for prostate cancer.

Current correlative studies, the target of Objective 2, can be found in the last column to the right in Table 2. Targeted correlative studies remain an important part of all new prostate cancer clinical trials at the University

of Michigan. A more detailed description of the correlative studies presented to the DOD-PCCTC by the University of Michigan is presented later in this report.

Table 2. Current areas of research by stage of disease, including correlative research

Current University of Michigan DOD-PCCTC Prostate Cancer Clinical Trials Summary					
Area of Focus	**Title**	**UM PI**	**Lead Site**	**Trial Status**	**Correlative Studies**
Neoadjuvant					
Signal transduction	2011.030, c09-041, A Randomized Trial of Preoperative GDC-0449 and Androgen Ablation Alone Followed by Radical Prostectomy for Select Patients with Locally Advanced Adenocarcinoma of the Prostate (NCI 8348)	Dr. Jeffrey Montgomery	MDACC	**Administratively closed by CTEP effective 3/31/2012**. Study terminated at UM 7/30/12.	Analyze tumor specimens for changes in hedgehog and androgen signaling, proliferation, apoptosis and markers linked to progression between the two arms; collect and archive tissue from the primary tumor, bone marrow biopsy/aspirate and blood (serum, plasma) for future studies.
Signal transduction	2011.008, c10-080, A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer	Dr. Daniel Hamstra	**University of Michigan**	Study activated 10/19/12. Closed to accrual 4/3/14.	To assess PTEN axis, the following biomarkers will be analyzed by IHC analysis; PTEN, Akt, Phos-Akt (Ser 473), Phos-Akt (Thr 308), p70S6K, Phos-p70S6K (Thr421/Ser424), 4EBP1, Phos-4EBP1, Stathmin; to evaluate putative markers of neo-angiogenesis and hypoxia, the following will be evaluated in tumor tissue before and after everolimus therapy; VEGF-A, HIF1-alpha, CD31 micro-vessel density.
Prostate (Rising PSA - Androgen Dependent)					
Angiogenesis/Signal Transduction	2007.086, c09-024, A Randomized, Phase II Study of GW786034 (Pazopanib) in Stage D0 Relapsed Androgen Sensitive Prostate Cancer Following Limited GnRH Agonist Therapy	Dr. Maha Hussain	Chicago	**Closed permanently 4/20/2010 due to multiple early patient discontinuations**. Study terminated 3/29/11.	N/A
Prostate (Rising PSA - Androgen Independent)					
AR signaling/Signal Transduction	2009.091, c07-044, A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration	Dr. Maha Hussain	**University of Michigan**	Closed to accrual 6/17/2011 at UM, closed 7/31/2011 study wide by Millennium, completed accrual.	Evaluate changes in bone turnover markers, assess archival tumor samples for candidate biomarkers including the TMRSS2/ERG fusion gene, characterize

	Resistant Prostate Cancer and a Rising PSA			Study terminated 2/19/13.	biomarkers in CTC's.
Metastatic Androgen Dependent Front Line					
Apoptosis/Signal Transduction	2008. 064 c07-012 A Phase II Study of AT101 to abrogate BCL-2 Mediated Resistance to Androgen Ablation Therapy in Patients with Newly Diagnosed Stage D2 Prostate Cancer. NCI 8014	Dr. Maha Hussain	CINJ	Met accrual goal, closed 9-14-10. Study terminated 3/17/11.	Determine changes in Bcl-2 and BAX/BAK protein expression in peripheral blood mononuclear cells and in baseline tumor tissue.
Apoptosis/Signal Transduction	2010.038, c09-038, Phase II Randomized Study of Bcl-2 Inhibition with ABT-263 Combined with Androgen Ablation Therapy in Newly Diagnosed Metastatic Prostate Cancer	Dr. Maha Hussain	CINJ	**Study on hold by sponsor as of 9-24-2010. UM Site withdrew participation 4/22/2011**.	DNA samples to be analyzed for genetic factors contributing to response to in terms of PK, tolerability and safety; circulating tumor cells concentrations at screening baseline and on therapy (at baseline assessed for Bcl-2 family proteins and gene copy number).
AR signaling/Signal Transduction	2013.117, c13-123, A Randomized Phase II Study of PD 0332991 AND Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer	Dr. Maha Hussain	**University of Michigan**	Expect to activate at UM in June 2014.	Biopsy tissue will be examined, using IHC, for total Rb, phosphorylated Rb, Cyclin D1, Cyclin D1B, Cyclin D3, CDK4, p16 (which is elevated in Rb-deficient tumors), and key Rb target genes, such as Cyclin A and MCM7. If adequate tissue is present, micro dissection will be performed and RNA submitted for transcriptomic/RNA-sequencing analysis.
Metastatic Androgen Independent Front Line					
Angiogenesis/ (Hedgehog) Signal Transduction	2009.042, c09-033, A Randomized Phase II Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer	Dr. David Smith	JHU	Met accrual goal, closed 10-1-2010. Study terminated 7/16/12.	To investigate changes in Itraconazole PK, serum testosterone, DHEA-S, ACTH, serum cortisol, aldosterone, and VEGF levels with time, changes in GLi1 mRNA expression levels and advanced MRI parameters with time.

Angiogenesis/Bone	2010.108, c09-057, A Randomized Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Asymptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	Dr. Maha Hussain	**University of Michigan**	Opened at UM site 6/9/2011. Closed to accrual 10/23/12. Met accrual goal study wide.	Serum PK, mRNA levels in whole blood or tumor samples, change in circulating endothelial cell count in whole blood with clinical outcome or other drug markers.
Signal Transduction	2010.005, c09-048, Phase I/II Trial of Anti-IGF-IR Monoclonal Antibody IMC-A12 plus mTOR Inhibitor Temsirolimus (CCI-779) in metastatic castration-resistant prostate cancer (CRPC). NCI #8417	Dr. Maha Hussain	MSKCC	**Closed 3-4-2011 by lead site (MSK) because of toxicities**. Terminated effective 3/17/11.	CTC analysis, PET imaging, tumor biopsy to evaluate biomarkers.
Cytotoxic Therapy (taxane derivative)	2011.016, c10-071, A Phase II study of single-agent tesetaxel in chemotherapy-naïve and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer	Dr. Maha Hussain	MSKCC	Activated at UM site on 10/21/2011. **As of 8/3/12, company in receivership. Sponsor filing for bankruptcy.**	N/A
Angiogenesis/Signal Transduction	2009.076, c11-079, A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	Dr. David Smith	**University of Michigan**	Phase II prostate cohort opened to all participating sites as of 11/18/2011. Closed to enrollment 2/29/12.	MRI, CT scan, and/or bone scans; PK; pharmacodynamic biomarkers (eg, sMET, HGF, VEGF-A, PlGF, sVEGFR2); tumor samples assayed for signaling pathways; CTCs; genotyping /single nucleotide polymorphism analysis (pharmacogenomics); markers of bone turnover, serum NTx, CTx, and bone alkaline phosphatase
AR Signaling	2011.052, c10-072, An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Advanced Castration-Resistant Prostate Cancer	Dr. David Smith	MSKCC	Activated at UM site on 12/19/2011. Closed to accrual 5/27/12. Met accrual goal.	Pre- and post-therapy changes in CTC number and molecular profiles in CTC.
Cytoxic therapy (Docetaxel nanoparticles)	2013.040, c12-111, An Open Label, Multicenter, Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable	Dr. Ajjai Alva	MSKCC	Activated at UM site on 8/23/2013.Sponsor held enrollment 11/16/13 (close to	Circulating tumor cells (CTCs) will be collected at selected sites Archival tumor samples for patients whose primary tumor was collected at time of their original cancer diagnosis will

	Suspension), Administered to Patients With Metastatic Castration-Resistant Prostate Cancer			accrual goal).	be analyzed in order to determine the level of PSMA expression
AR signaling/Signal Transduction	2011.012, c11-089, A Randomized Gene Fusion-Stratified Phase 2 Trial Of Abiraterone With Or Without ABT888 For Patients With Metastatic Castration-Resistant Prostate Cancer: NCI 9012	Dr. Maha Hussain	**University of Michigan**	NCI activated trial on 4/18/12. UM site activated 5/3/12.	•To determine the concordance in fusion status among prostate cancer samples from the primary site, biopsied metastasis, and circulating tumor cells (CTCs). •To assess if ETS fusion status in the CTCs **at baseline, 12 weeks and at disease progression** is associated with response to therapy. •To evaluate if the number of CTCs, as well as the expression levels of the androgen receptor, PTEN, RAD51, and gamma-H2aX foci in the CTCs at baseline, 12 weeks and at disease progression in all patients is associated with response to therapy. •To determine the role of PTEN loss as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888. •To determine the role of PARP1 activity as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888. •To perform next-generation sequencing for discovery of novel gene fusions in prostate cancers negative for ETS fusions. •To perform germline single nucleotide polymorphism (SNP) analysis of genes involved in hormone synthesis, transport, binding,

					metabolism, and degradation for discovery of novel SNPs predictive of response to abiraterone, alone or in combination with ABT-888. •To determine if ETS fusion RNA levels in blood are predictive of response to abiraterone, alone or in combination with ABT-888.
Metastatic Androgen Independent After Docetaxel					
Signal Transduction (DNA repair)	2009.114, c09-031, A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temzolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease	Dr. Maha Hussain	**University of Michigan**	Closed 10/22/10 met accrual goal. Study terminated 12/13/11.	Exploratory research to find biomarkers that may serve as surrogates for clinical endpoints in future ABT-888 studies or that may be predictive of ABT-888 activity will be conducted. Blood samples will be collected at designated time points throughout the study. Archived tissue samples (if available) will be collected while subjects are on study.
Signal Transduction/ Cytotoxic Therapy	2010.039, c09-025, Phase II trial of carboplatin and RAD001 in metastatic castrate resistant prostate cancer (CRPC) pretreated with docetaxel therapy	Dr. David Smith	Wayne State	**Novartis withdrew support on 5/18/2011.** Trial terminated 6/23/11.	Phospho mTOR status of prostate cancer in archival tissue, PK response predictors ($p70^{s6}$/$p70^{s6}$ phosphoprotein, AKT/pAKT), PK of the 2 drugs in ~ 50% of patients.
Cytotoxic Therapy	2008.033, c08-009, A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301)	Dr. Maha Hussain	MDACC	**Closed by 2/1/11 by Celgene**. Trial terminated 1/8/14.	PK samples to determine caveolin-1 levels
Angiogenesis/Signal Transduction	2011.067, c10-073, A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with the Combination of Cediranib (AZD2171) plus BMS-354825 (Dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer: NCI 8476	Dr. David Smith	JHU (Princess Margaret Hospital)	Activated at UM site on 10/20/2011. **On-hold to accrual effective 2/14/12 due to NCI budgetary restrictions and closed due to the discontinuation of cediranib development by the sponsor**. Study permanently closed to accrual 12/31/12.	Bone resorption markers (e.g. c-telopeptide and bone alkaline phosphatase), and how these biomarkers correlate with clinical outcome.

Monoclonal Antibodies mAB) for Cytotoxic Therapy	A Phase 2, open-label, multicenter study of PSMA ADC in subjects with castration-resistant metastatic prostate cancer (CRMPC	Dr. David Smith	JHU	Activated at UM site on 03/28/13 4/21/14-enrollment closure by sponsor.	PSMA expression evaluated by IHC and on circulating tumor cells (CTCs) by immunofluorescence; serum analysis of chromogranin (CgA) and neuron-specific enolase (NSE).
AR signaling/Signal Transduction	A Phase Ib, Open-Label, Dose-Escalation Study of the Safety and Pharmacology of GDC-0068 in Combination with Docetaxel, Fluoropyrimidine Plus Oxaliplatin, Paclitaxel, or Enzalutamide in Patients with Advanced Solid Tumors	Dr. Maha Hussain	**University of Michigan**	Activated at UM site on 01/28/14.	• To characterize the pharmacokinetics of GDC-0068 and its metabolite G037720, and enzalutamide and its metabolite. • To explore the potential relationship between PI3K pathway genetic alterations, such as PI3K mutations and PTEN loss identified in archival tumor tissue, circulating tumor cells, and/or tumor DNA isolated from blood, and any anti-tumor activity observed during this study.
Cytoxic Therapy with bone-targeted alpha particle emitting nuclide.	A Three Arm Randomized Open-Label Phase II Study of Radium-223 Dichloride 50kBq/kg and Versus 80 kBq/kg Versus 50 kBq/kg in an Extended Dosing Schedule in Subjects with Castration-Resistant Prostate Cancer Metastatic to the Bone.	Dr. Maha Hussain	**University of Michigan**	Expect to activate at UM in July 2014.	

With regards to objective #3, the University of Michigan has developed and maintained successful collaborative efforts. The University of Michigan has maintained a successful membership in the University of Chicago N01 Phase II Consortium sponsored by the Cancer Therapy Evaluation Program (CTEP), of the Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute (NCI) (http://www.cancer.gov/). The major emphasis of this consortium is on Phase II studies and pilot protocols that explore promising single agent and combination therapies, and high priority studies that are pivotal for drug development and require rapid initiation, completion, and data reporting. These groups provide a valuable addition to our group's other diverse collaborative research networks including: the PCCTC, and National cooperative groups (SWOG, RTOG, ECOG) and can particularly synergize with the DOD-PCCTC. Successful collaborations, we believe, are the first step towards implementing the Coordinating Center's plan for the financial self-sufficiency of the consortium by the end of the award period.

Task #2: We will collect and analyze blood, urine and tissue samples collected on all the consortium clinical trials that are led by the University of Michigan. (Sample Collection: Months 1-48), (Analysis: Months 48-60).

Sample collection for the correlative endpoints for the clinical trials are progressing, please see

correlative studies column of Table 2 for a list of ongoing correlative research included in the DOD-PCCTC trials and Table 3 for a breakdown of the samples that have been collected for DOD-PCCTC trials thus far. Analysis for some of the trials has been initiated and completed (please refer to abstracts in the Appendix).

Please see the following scientific correlative objectives for four studies introduced to the DOD-PCCTC by the University of Michigan that highlight the scope of our efforts in this area:

1. **A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA** (trial was activated at our site on 4-8-2010):
    - To evaluate changes in markers of bone turnover (urine N-telopeptide, serum bone specific alkaline phosphatase, serum osteoprotegerin, and others) for possible correlation with changes due to androgen deprivation and/or bone metastases.
    - To enumerate circulating tumor cells (CTC).
    - To assess archival tumor specimens for candidate biomarkers predictive of TAK-700 antitumor activity including, but not limited to, the *TMPRSS2*:*ERG* fusion gene.
    - To quantify the interval between PSA progression and development of metastatic disease.
    - To assess the relationships between TAK-700 exposure and pharmacodynamic and clinical endpoints.
    - To assess possible changes in androgen-deprivation related symptoms in patients treated with TAK-700.

2. **c09-057, A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)** (site activated 6/9/2011)

    - Serum concentration data and PK parameters of EMD 525797 derived from non-compartment analysis;
    - Population PK of EMD 525797;
    - Candidate cell type counts, proteins or metabolites circulating in the blood and/or expressed by the tumor or change in concentrations and their and their relationship to the clinical outcome and/or drug activity markers.
    - Individual genetic variations in the host genome and/or in the tumor genome or between them and the clinical outcome and/or drug activity markers.
    - mRNA levels or change in mRNA levels in whole blood and/or tumor samples associated to the clinical outcome and/or drug activity markers.
    - Protein or metabolite concentrations or change in concentrations in urine and the clinical outcome and/or drug activity markers.
    - Exploring the relationship of the count or change in count of circulating endothelial cells measured in whole blood with the clinical outcome and or drug activity markers

3. **c11-089, NCI 9012, A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer.** (NCI activated site 4/18/12)
   Correlative Objectives
    - To determine the concordance in fusion status among prostate cancer samples from the primary site, biopsied metastasis, and CTCs.
    - To assess if ETS fusion status in the CTCs is associated with response to therapy.
    - To evaluate changes in circulating tumor cells (CTCs) at baseline and during therapy in all patients.

- To determine the role of PTEN loss as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
- To determine the role of PARP1 activity as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
- To perform next-generation sequencing for discovery of novel gene fusions in prostate cancers negative for ETS fusions.
- To perform germline single nucleotide polymorphism (SNP) analysis of genes involved in hormone synthesis, transport, binding, metabolism, and degradation for discovery of novel SNPs predictive of response to abiraterone, alone or in combination with ABT-888.
- To determine if ETS fusion RNA levels in blood are predictive of response to abiraterone, alone or in combination with ABT-888.

4. **c13-123, A Randomized Phase II Study of Androgen Deprivation Therapy with or without PD 0332991 in RB-Positive Metastatic Hormone-Sensitive Prostate Cancer** (expect site activation mid to late May 2014)
   Correlative Objectives:
   - To determine whether cyclin D1, cyclin D1B, p16, CDK4, E2F1, Cyclin A, MCM7, or Ki67 levels in pretreatment metastatic tumor biopsy tissue predict a subset of tumors responsive to PD 0332991 or overall response rates.
   - To evaluate tumor transcriptome and mutational signatures to identify biomarkers which predict response to PD 0332991.
   - To create a tissue repository consisting of hormone-sensitive metastatic prostate cancer specimens with associated RB status and clinical data which can be used to correlate RB status with general clinical outcomes and explore and validate important genes identified above.

Table 3: Samples collected for DOD-PCCTC correlative studies to date

Correlative Studies Sample Collection		
DOD Number	Study Title	Samples Collected to date
c08-009	A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301)	97 Serum Sets
c09-031	A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temzolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease	44 Whole Blood CTC Samples 6 Whole Blood Pharmacogenetic Samples 144 Plasma Sets 22 Serum Sets
c09-033	A Randomized Phase II Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer	14 Skin Biopsy Samples 62 Plasma Sets 90 Whole Blood CTC samples
c09-044	A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA	33 Whole Blood CTC Samples 26 Urine Sets 51 Hematology Samples 198Serum Sets 114 Plasma Sets
c09-057	A randomized, double-blind, placebo-controlled, multicenter Phase II trial investigating two doses of EMD 525797 in subjects with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (mCRPC)	25 Immunogenicity samples 31 Pharmacokinetic Samples 4 DNA Biomarker Pharmacogenetic Samples 22 mRNA samples 23 Urine Biomarkers 26 Protein biomarkers 19 CTC samples
c10-073	A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with theCombination of Cediranib (AZD2171) plus BMS-354825 (dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer	10 Serum Sets

c10-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	16 Sets of Archived Tumor Blocks/Slides 23 Whole Blood CTC Samples 59 Hematology Samples 29 Whole Blood Pharmacogenetic Samples 25 Reticulocyte Count Samples 100 Serum Sets 343 Plasma Sets 20 Urine
c11-089	A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer	112 biopsy samples 94 Pharmacogenomic SNP samples 94 TMPRSS2-ERG mRNA Samples 106 CTC samples
c12-104	An Open Label, Multicenter, Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension), Administered to Patients With Metastatic Castration-Resistant Prostate Cancer	3 archived biopsy samples 20 CTC samples
c12-111	A Phase 2, open-label, multicenter study of PSMA ADC in subjects with castration-resistant metastatic prostate cancer (CRMPC)	43 CTC samples 34 Hematology samples 35 Urine samples 4 PBMC samples 216 Serum samples
c134-135	A Phase Ib, Open Label, Dose Escalation Study of the Safety and Pharmacology of GDC 0068 in Combination with Docetaxel, Fluororpyrimidine plus Oxaliplatin, Paclitaxel, or Enzalutamde in Patients with Advanced Solid Tumors	8 CTC Samples 5 CT DNA Samples 2 Pharmacogenetic Samples 22 PK Sets 7 PSA Samples

Task #3: Final Analysis and Report Writing. A final clinical and statistical analysis of all data (clinical and correlative) on all University of Michigan led trials will be undertaken. A final report and draft manuscripts will be circulated to all co-authors and submitted to appropriate scientific journals for publication. (Months 54-60).

Year 1 (01 Apr 2009 – 31 Mar 2010)
We were in the process of analyzing and reporting previously completed trials.

Year 2 (01 Apr 2010 – 31 Mar 2011)
The results of the c08-001 trial (IMC-A12 and IMC-1121B) were reported by Dr. Hussain at the 2011 IMPaCT meeting **(Appendix B)**. Final reporting is awaiting mature survival data. A draft manuscript for the c05-007 study (cilengitide non-met) was circulated to all co-authors and a manuscript was submitted and subsequently published in the journal *Investigational New Drugs* in November 2010 **(Appendix AA)**.

Year 3 (01 Apr 2011 – 31 Mar 2012)
The results of the c08-001 trial (IMC-A12 and IMC-1121B) and the c09-031 trial (ABT-888) were reported by Dr. Hussain at the 2012 GU ASCO meeting **(Appendix I and J).** Results of the c09-044 trial (TAK-700) were reported by Dr. Hussain at the 27th EAU Congress meeting 2012 **(Appendix M)**. Final reporting is awaiting mature survival data.

Year 4 (01 Apr 2012 – 31 Mar 2013)
The results of the c11-079 trial (XL-184 NRE) were reported by Dr. Smith and the results of the c09-044 trial (TAK-700) were reported by Dr. Hussain (Senior-author) at the 2012 Annual ASCO meeting **(Appendix N and O).** Final reporting is awaiting mature survival data. For all other completed trials we are awaiting more mature survival and efficacy data before publishing the results. Dr. Smith was first author on a manuscript publishing the results of the c11-079 trial (XL184-Cabozantinib) **(Appendix DD)**. The results of the c09-033 Itraconazole study were also published with Dr. Smith as a co-author **(Appendix EE).**

Year 5 (01 Apr 2013 – 31 Mar 2014)
The results of the c09-031 trial (ABT-888) were published in the journal *Investigational New Drugs* on April 26, 2014 by Dr. Hussain (First author) **(Appendix FF)**. Results of the c12-111, PSMA ADC 2301 trial were presented as both an abstract and poster at the 2014 ASCO GU Cancers Symposium meeting **(Appendix R)** and as a poster at the 2014 ASCO Annual meeting **(Appendix T)**. Preliminary results of the c11-089 (gene fusion) trial were accepted for presentation at the 2014 ASCO annual meeting as a poster **(Appendix S)** and as a publication-only abstract **(Appendix V- available only online)**. Results of the c09-057 (EMD 525797) trial were accepted for presentation at the 2014 Annual ASCO meeting **(Appendix U)**. A draft manuscript for the c09-044 study (TAK-700) was circulated to all co-authors and a manuscript was submitted to the journal *Clinical Cancer Research* in April 2014. We are currently awaiting the reviewer's decision on the manuscript. Dr. Smith was co-author on two manuscripts reporting the results of two PCCTC trials (c11-079, XL184 NRE) in *European Urology*, **(Appendix GG)** and (c10-073, Cediranib ± Dasatinib, in *Investigational New Drugs*, **(Appendix HH)**. The results of the c08-001 (IMC-A12/IMC-1121B) trial are being finalized and will be submitted to the *Journal of Clinical Oncology* this month (May 2014).

As part of their SOW, each participating site was expected to present at least 1 clinical trial each year for the consortium's consideration.

At the end of the fifth year of DOD-PCCTC funding from the 2009 Clinical Consortium Award, ten studies with novel drugs have been introduced to the DOD-PCCTC by the University of Michigan. Three of these trials (c13-123, Palbociclib; c13-127, Radium-223; and c14-135, GDC-0068) were introduced to the DOD-PCCTC during the fifth year of the award (4/1/2013-3/31/2014). The trials are as follows:

The following are the two trials that were presented by University of Michigan to the consortium and accepted for consortium participation during our first year of participation; 2009-2010 (see Table A for the list of trials introduced to the consortium by the University of Michigan and their current accrual numbers):

1. **c09-031 A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temozolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease (LOI circulated 2/25/09).**
   ABT-888 is a potent Poly(ADP-ribose)-polymerase (PARP) inhibitor that delays the repair of DNA damage induced by chemotherapeutics. PARP is a nuclear enzyme that recognizes deoxyribonucleic acid (DNA) damage and facilitates DNA repair[1]. PARP activity is essential for the repair of single-stranded DNA breaks through the base-excision repair (BER) pathways[2-4] and is an important modulator of double-stranded break repair pathways. Consequently, inhibition of PARP activity should enhance the effects of DNA-damaging agents, including alkylators, platinums, topoisomerase poisons, and radiation therapies on tumor cells. Pre-clinical data in a variety of tumor cells including both an orthotopic and bone metasasis model of prostate carcinoma, suggest the addition of ABT-888 to temozolomide profoundly improves the anti-tumor response and that ABT-888 could reverse resistance to temozolomide. Temozolomide is a newer generation DNA methylating agent that crosses the blood brain barrier. It is Federal Drug Administration (FDA) approved for the treatment of central nervous system (CNS) tumors and melanoma.
   This will be an open-label single arm study evaluating the safety and efficacy of ABT-888 in combination with temozolomide (TMZ) as a second or third line treatment in subjects with castration resistant prostate cancer (CRPC). The study population will be patients with histologically or cytologically confirmed metastatic castration resistant prostate cancer with measurable and/or bony disease who have progressed despite androgen deprivation therapy and have had at least one and no more than two prior systemic non-hormonal therapies (at least one must include docetaxel) for castration resistant metastatic disease.
   The primary objective will be to assess whether the combination of ABT-888 with temzolomide (TMZ) has activity in subjects with metastatic castration resistant prostate cancer (CRPC) as reflected by the PSA response. Secondary objectives include evaluating the safety and tolerability of combining ABT-888 and temozolomide (TMZ) in subjects with metastatic castration resistant prostate cancer (CRPC), assessing the objective response rate (ORR), PSA decline rate, time to progression (TTP), progression free survival (PFS) and overall survival (OS) and determining the effects of ABT-888 treatment on the level of PARP inhibition and DNA damage in peripheral blood mononuclear cells (PBMCs) and tumor cells.
   We were the lead site for the c09-031 study which was a proof of principle pilot study looking at the combination of ABT-888 (an oral PARP inhibitor) with temozolomide in patients progressing on up to two prior therapies for castration-resistant disease. Dr. Hussain was involved in the trial design of this study with the sponsors. This trial completed accrual in October 2010. Six of the twenty–four patients accrued to this study were from our site

2. **c07-044, A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA (LOI circulated 7/9/09).**

   TAK-700 is a selective and potent inhibitor of 17, 20-lyase, a key intermediary in the adrenal androgen and testosterone synthesis pathway. This action makes it a good candidate for development in castration-resistant prostate cancer (CRPC) where persistent extra-gonadal synthesis of weak but still effective adrenal androgens (dehydroepiandrosterone [DHEA] and androstenedione) and testosterone, occurring either in the adrenal cortex or tumor cells, ultimately results in PSA progression and detectable metastases. The specificity of TAK-700 for 17, 20-lyase enzymatic activity over 17-hydroxylase activity may afford it a safer toxicity profile than agents such as abiraterone that inhibit both steps in the testosterone synthesis pathway, affecting cortisol precursor synthesis. By disrupting the synthesis of

testosterone but potentially not that of cortisol, TAK-700 could offer a more favorable therapeutic index in CRPC.

This multicenter phase 2 open-label single-arm study will evaluate the safety and efficacy of TAK-700 in patients with CRPC without radiographic evidence of metastases who have a rising PSA. The primary endpoint, assessed after 3 months of TAK-700 administration, is the percentage of patients achieving a PSA reduction to ≤0.2 ng/mL. Secondary endpoints include PSA response rates (30%, 50%, and 90% PSA declines), the percentage of patients who achieve a PSA ≤0.2 ng/mL following 6 months of TAK - 700 treatment, time to PSA progression, time to metastases, duration of progression-free survival, endocrine markers, and standard safety parameters. Exploratory endpoints include bone turnover markers, CTC counts, and candidate TAK-700 biomarkers assessed in archival tumor specimens. Enrolled patients will be treated with TAK-700 until evidence of PSA or disease progression.

The following were the three trials that was presented by University of Michigan to the consortium and accepted for consortium participation during our second year of participation, 2010-2011.

3. **c09-057, A Randomized Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Asymptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC). (LOI circulated 12/11/09 and 4/28/10).**

   This is an exploratory, randomized, double-blind, placebo-controlled, multi-center Phase II trial investigating two EMD 525797 dosing regimens in asymptomatic or mildly symptomatic mCRPC subjects. Dr. Husain was heavily involved in the design of this study with the sponsor. EMD 525797 is a de-immunized monoclonal IgG2 antibody antagonist directed against the alpha-v (αv) subunit of human integrin receptors. EMD 525797 binds specifically to the αv-chain, thereby inhibiting ligand binding to all αv-heterodimers (αvß1, αvß3, αvß5, αvß6, αvß8). αv-integrins are highly expressed in angiogenic, proliferating tumor blood vessels and on certain types of tumor cells. In addition, in a limited set of tumors, increased expression of αvß3 is associated with increased cell invasion and metastasis [5]. It has been demonstrated that members of the αv-integrin family play a direct role in tumor progression, tumor angiogenesis and metastasis [6]. Histochemical data [7]and *in vitro* studies on colorectal cancer (CRC) cell lines, prostate cancer cell lines, endothelial cells and osteoclasts have shown that αv-integrins are expressed on the tumor vasculature, tumor cells and osteoclasts [7-9].

   The primary objective of the trial is to evaluate whether two dose levels of EMD 525797 administered as 1 hour I.V. infusion every 3 weeks is superior to standard of care (SoC) as assessed by progression free survival time (PFS) in subjects with asymptomatic or mildly symptomatic mCRPC . Secondary objectives are to evaluate the efficacy, safety profile, and pharmacokinetic (PK) profile of EMD 525797 and evaluate changes in circulating tumor and endothelial cells (CTCs).

4. **c11-079, A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors. (LOI circulated 1/5/11).**

   This is a Phase 2 study to evaluate the efficacy and safety of XL184 in subjects with selected advanced tumor types. XL184 is a small molecule which inhibits multiple receptor tyrosine kinases. Its primary targets include MET, VEGFR2 and RET which play critical roles in angiogenesis and tumor cell proliferation, invasion, and metastasis. In preclinical studies XL184 has rapid effects on endothelial cells resulting in vascular breakdown and tumor cell death within 24 hours after administration.

   These changes translate into significant tumor growth inhibition or tumor regression in multiple xenograft tumor models including human lung, breast, thyroid, and brain cancer. In addition, XL184 results in a substantial reduction in tumor invasiveness and metastasis in the RIP-Tag2 mouse model of pancreatic neuroendocrine cancer. In phase I studies XL184 demonstrated good oral availability with a half-life of 80-90hours and tolerable toxicity profile. The most common adverse events were fatigue, diarrhea, anorexia, rash, and palmar-plantar erythrodysesthesia (PPE) syndrome. In terms of activity, almost 40% of patients showed stable disease greater than 3 months with several up to 6 months while on treatment.[10,11]

   Based on target rationale and observed anti-tumor activity in early clinical studies, a phase III trial is ongoing in medullary thyroid cancer and phase II studies are ongoing in glioblastoma, prostate cancer,

ovarian cancer, non-small cell lung cancer, and several other solid tumors. The current trial of XL184 in patients with advanced prostate cancer has shown significant effects on bone lesions in patients both pre- and post-therapy with docetaxel Subjects were enrolled into one of nine tumor type cohorts (including prostate). All cohorts will initially follow the Randomized Discontinuation Trial (RDT) design. Based on periodic review of all available data, enrollment into specific cohorts may be halted, continued within the RDT design, or closed in favor of opening open label non-randomized expansion (NRE) cohorts. Because of early promising data, the accrual was stopped and a phase II expansion cohort for prostate cancer patients was introduced to the PCCTC by Dr. Smith in December 2010.
We propose to conduct a phase II trial aiming at estimating the efficacy of XL184 in chemotherapy-naive patients with CRPC and bone metastases and characterize the effects of XL184 on prostate cancer bone lesions using novel methods to assess bone metabolism and tumor activity. The primary endpoint of the trial will be to assess the proportion of patients who do not exhibit disease progression, and thus achieve clinical benefit from the agent. Correlative studies will include assessment of several biomarkers of bone metabolism, which are present in serum and bone. At the same time, information about tumor activity in the bone will be obtained via imaging with diffusion MRI. We are currently enrolling CRPC patients at our site and four other DOD-PCCTC institutions with three additional member institutions to join in the prostate expansion cohort for this study. Dr. Smith presented preliminary data from the open label Lead-in Stage of the ongoing adaptive design phase II randomized discontinuation trial of XL184 at the 2011 ASCO GU Cancers Symposium and the 2010 EORTC-NCI-AACR Symposium on Molecular Targets and Cancer (see Appendix E and F). It showed that 13 of the 15 patients (87%) with known bone metastases had either complete or partial remission of the lesions on bone scan. Multiple cases of complete or near complete resolution were observed in both docetaxel and docetaxel-naïve subgroups. Dr. Hussain will give an oral presentation of the final data on XL184 in these patients at the 2011 Annual ASCO meeting Prostate Cancer session **(Appendix G)**.
c11-079 is the Phase II expansion cohort of the randomized discontinuation trial of XL184 in solid tumors introduced to the PCCTC by Dr. David Smith. Dr. Smith and Dr. Hussain were involved in designing the expansion phase of this study with the sponsor. Seven other PCCTC institutions are participating in this trial.

5. **c11-080, A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer. (LOI circulated 2/10/11).** Prostate cancer exhibits significant heterogeneity in genetic make-up, however, inactivation of the Phosphatase and Tensin homolog deleted on chromosome 10 (PTEN) tumor suppressor gene is one of the more common events occurring in as many as 20-25% of all prostate cancers and is more common in high-grade tumors. PTEN loss has been associated with higher Gleason grade, higher pathologic stage, increased biochemical failure, and radiation resistance. Further, tumor hypoxia, which is common in prostate cancer, is a major determinant of both radiation resistance and prostate cancer recurrence. The mammalian target of rapamycin (mTOR) is a critical player in both prostate tumor pathophysiology and neo-vascular growth. In preclinical models tumors mutant in PTEN have increased levels and activity of mTOR and are sensitive to mTOR inhibitors while inhibition of the mTOR pathway has also been demonstrated to inhibit tumor neo-angiogenesis. As a result the combination of radiation therapy and mTOR inhibition has been demonstrated to radiosensitize both PTEN null and PTEN wild-type tumors through actions directed at both tumor and vascular cells. Therefore, we are conducting a phase I trial using a time-to-event continual re-assessment model (TITE-CRM) to evaluate the safety of adding the mTOR inhibitor, everolimus (RAD001, Afinitor), to hormonal therapy and radiation therapy for high-grade or locally advanced prostate cancers. In addition, following a lead in with everolimus we will evaluate biomarkers for tumor and vascular response to ascertain the extent of inhibition achieved at the maximally tolerated dose. This treatment represents a novel targeted method to address known mechanisms of resistance to the current standard therapy and has the potential to significantly improve clinical outcomes. If this study achieves its goal of identifying an appropriate dose of Everolimus which is safe within the protocol specified definition and achieves pharmacodynamic evidence for suppression of the Akt/mTOR/PTEN signaling pathway then it will have been deemed a success and a larger confirmatory Phase 2 study could be undertaken at the identified dose level. Three other DOD-PCCTC

member institutions will be participating in this study with The University of Michigan as the lead site. The pre-clinical work leading to the development of this protocol was supported by Novartis Pharmaceuticals and an ASCO Career Development award.

The following are the two trials that was presented by University of Michigan to the consortium and accepted for consortium participation during our third year of participation, 2011-2012

6. c11-089 - **A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer. (LOI circulated 8/10/11).** This study is an investigator initiated CTEP sponsored biomarker stratified and randomized phase II trial that will evaluate the role of ETS gene fusion as a predictive biomarker for response to hormone therapy alone or hormone therapy plus PARP-1 targeted therapy in patients with mCRPC. The study will also evaluate whether the addition of PARP-1 targeted therapy is superior to hormone therapy based on gene fusion status. The scientific rationale for this study is supported by:

   1. Abiraterone is FDA approved based on prolonging survival in patients with mCRPC post docetaxel; however the effect is modest and not all patients benefit.
   2. ETS gene fusions are predominantly driven by an androgen-sensitive promoter. Data from radical prostatectomy series suggest that ETS fusion status predicts for response to adjuvant androgen deprivation therapy[12]and preliminary data from phase I/II studies of mCRPC patients suggest that abiraterone may have greater therapeutic effect in ETS-fusion positive prostate cancer patients. [13,14]
   3. There is interaction of PARP1 with the androgen signaling cascade, regardless of ETS fusion status and with ETS fusions; our data indicate that ERG-positive xenografts are preferentially sensitive to PARP-1 inhibitors.
   4. ABT-888 has been demonstrated to have efficacy across a wide range of tumor types in preclinical studies.[15] ABT-888 has been demonstrated to inhibit PARP1 in a clinical phase 0 study, and is currently being assessed as a component of combination therapy across a range of tumor types clinically, including breast, liver, and ovarian cancer, as well as an unselected metastatic prostate cancer population. We have conducted in collaboration with Abbott and the DOD-PCCTC, a clinical trial with ABT-888: M11-070 Protocol, A Phase II Study Combining ABT-888 (an Oral PARP Inhibitor) + Temozolomide in Patients with Metastatic Castration Resistant Prostate Cancer Who Have Failed Up to Two Non-hormonal Systemic Therapies (c09-031). The interim data suggests it's feasible to administer ABT-888 in combination and that there is a signal of clinical activity.

   - Primary Objectives
     - To evaluate the role of ETS gene fusion as a predictive biomarker for response to hormone therapy (abiraterone) alone or hormone therapy plus PARP-1 targeted therapy (ABT-888) in patients with metastatic castration resistant prostate cancer.
     - To evaluate whether the addition of PARP-1 targeted therapy is superior to hormone therapy alone based on ETS gene fusion status.
   - Secondary Objectives
     - Rate of PSA declines.
     - Objective response rate.
     - Progression-free survival.
     - Evaluate the qualitative and quantitative toxicity of abiraterone acetate with and without ABT-888.
   - Correlative Objectives
     - To determine the concordance in fusion status among prostate cancer samples from the primary site, biopsied metastasis, and CTCs.
     - To assess if ETS fusion status in the CTCs, at baseline, 12 weeks, and at disease progression (or when off study) is associated with response to therapy.
     - To evaluate if the number of circulating tumor cells (CTCs), as well as the expression levels of androgen receptor, RAD51, and gamma-H2aX foci in the

CTCs at baseline, at 12 weeks, and at disease progression in all patients is associated with response to therapy..

- To determine the role of PTEN loss as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
- To determine the role of PARP1 activity as a predictive biomarker of response to abiraterone, alone or in combination with ABT-888.
- To perform next-generation sequencing for discovery of novel gene fusions in prostate cancers negative for ETS fusions.
- To perform germline single nucleotide polymorphism (SNP) analysis of genes involved in hormone synthesis, transport, binding, metabolism, and degradation for discovery of novel SNPs predictive of response to abiraterone, alone or in combination with ABT-888.
- To determine if ETS fusion RNA levels in blood are predictive of response to abiraterone, alone or in combination with ABT-888.

The University of Michigan is the lead site, with the University of Chicago acting as the coordinating center for this multicenter study. Thirteen sites in the US are participating in the trial. 148 subjects will be randomized. This trial will be conducted as part of the University of Chicago Phase II Consortium sponsored by CTEP and through the Department of Defense (DOD) Prostate Cancer Clinical Trials Consortium (DOD-PCCTC). Six other DOD-PCCTC member sites are participating in this study (Johns Hopkins University, MD Anderson Cancer Center, University of Wisconsin, Cancer Institute of New Jersey, University of Washington, and the University of Chicago). CTEP approved and activated this study on 3/30/2012 and our site was activated on 4/18/2012. This trial is one of the lead trials selected to be part of the Stand Up to Cancer (SU2C) – Prostate Cancer Dream Team Translational Cancer Research Grant (AACR/PCF).

The following are the three trials that were presented by University of Michigan to the consortium and accepted for consortium participation during our fifth year of participation, 2013-2014

7. **c12-111- PSMA ADC 2301 / A Phase 2, open-label, multicenter study of PSMA ADC in subjects with castration-resistant metastatic prostate cancer (CRMPC). (**LOI was submitted to the PCCTC on 11/14/2012 and was circulated on 3/13/13). This study is a Phase 2, open-label, multicenter study to assess the anti-tumor activity and tolerability of PSMA ADC in up to 75 subjects with castration-resistant metastatic prostate cancer (CRMPC). Patients must have received at least one, but no more than two cytotoxic chemotherapy regimens, one of which must have contained docetaxel. Patients must have received and progressed on abiraterone acetate and must have failed, refused, or not be a candidate for treatment with cabazitaxel than two, cytotoxic chemotherapy regimens, one of which must have contained docetaxel. The purpose of this phase 2 study is to assess the anti-tumor activity and tolerability of PSMA ADC in subjects with CRMPC.
PSMA is a 750-residue, type II, transmembrane glycoprotein that is highly expressed in prostate cancer cells and has limited expression in normal non-prostatic tissues. In normal prostate, PSMA is expressed predominantly as a variant (PSM') that is retained in the cytoplasm. However, in prostate cancer, PSMA is expressed as a membrane anchored, noncovalently associated homodimer possessing a large extracellular domain (707 amino acids), a hydrophobic transmembrane domain (24 amino acids), and a short cytoplasmic domain (19 amino acids).[16,17] The extracellular domain of PSMA possesses glutamate carboxypeptidase activity (EC 4.17.21), but the role of this activity in cellular transformation and metastasis is not understood. Dimerization is critical for enzyme activity[18] and recent crystal structures have revealed that the extracellular domain of PSMA has a compact dimer interface.[19-21] .PSMA bears no sequence or structural homology with PSA, which is a secreted protein and a member of the kallikrein family of serine proteases.
Although PSMA expression is highest in prostate, limited expression has been reported in normal brain, small intestines, liver, proximal kidney tubules, and salivary gland.[16,17,22,23] Immunohistochemistry (IHC) studies have reported that PSMA is largely localized to the cytoplasm in normal tissues.1,7,8

These findings are consistent with the observed tissue binding patterns of the PSMA mAb used in PSMA ADC. PSMA expression in cancerous prostate is approximately 10-fold greater than that in normal prostate. Expression in normal prostate is approximately 10-fold greater than that in the brain and is 50- to 100-fold greater than that in the liver or kidney. In most tissues, no expression of PSMA is observed.

The restricted pattern of expression of PSMA, its upregulation in advanced disease, and its membrane-bound nature combine to make this molecule potentially useful for the detection, management, and treatment of prostate cancer (reviewed in [24]).ProstaScint® (EUSA Pharma, Oxford, England) is an 111In-labeled form of a mouse mAb directed to PSMA (7E11) and has received FDA approval for the immunoscintographic detection and imaging of metastatic prostate cancer in soft tissues.[23,25-27] Because the 7E11 epitope is located in the cytoplasmic domain of PSMA, it is likely that this mAb localizes to regions of tumor necrosis in vivo.

In addition, several studies have demonstrated that PSMA is abundantly expressed on new blood vessels that supply most non-prostatic solid tumors, including lung, colon, breast, renal, liver and pancreatic carcinomas, as well as sarcomas and melanoma.[28,29]

Anti-body Drug Conjugates (ADCs) combine the molecular targeting of mAbs with the chemotherapeutic properties of potent cytotoxic drugs. Three critical elements of ADCs are the mAb, the cytotoxic drug and a linker for attaching the drug to the mAb. These elements of PSMA ADC are summarized below.

PSMA ADC is a fully human mAb directed to PSMA, which is linked to the potent antitubulin agent monomethyl auristatin E (MMAE). The PSMA mAb portion of PSMA ADC binds to the PSMA antigen to form a complex that is rapidly internalized. Upon internalization, the linker dipeptide is cleaved by human cathepsin B, a lysosomal protease, and unmodified MMAE is released inside the cell. Free MMAE results in the arrest of the cell cycle, leading to apoptotic cell death.

New therapies are urgently needed to expand therapeutic options and improve overall survival in CRMPC. One approach involves the use of monoclonal antibodies (mAb) to deliver a cytotoxic agent to the prostate tumor cells (antibody-drug conjugates [ADC]). Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein with particular features that render it an attractive target for cancer therapy, including ADC therapy. These include high expression in prostate cancer cells and limited expression in normal non-prostatic tissues, increased expression with disease progression, and the ability of the protein to be internalized. Internalization facilitates delivery of an ADC into the cell. In addition, PSMA is abundantly expressed on new blood vessels that supply most non-prostatic solid tumors. Thus, PSMA-linked therapy may be useful in treatment of solid tumors in general.

Data from this study will be used to estimate the anti-tumor response rates to PSMA ADC treatment and to continue to describe the safety profile of PSMA ADC for future trials. Response rates for the percent of subjects who were previously treated with docetaxel who achieved ≥ 50% decline from baseline PSA (PSA responders) when treated with subsequent therapies such as carboplatin or abiraterone have been reported. These response rates are in the range of 10% to 50%.[30-32]The University of Michigan will act as the lead site, with the Johns Hopkins University also participating in this multicenter study. This trial was activated at the University of Michigan site on 4/2/13 and eight patients have been registered to this trial.

8. c13-123, A Randomized Phase II Study of Androgen Deprivation Therapy with or without PD 0332991 in RB-Positive Metastatic Hormone-Sensitive Prostate Cancer. (LOI circulated 3/13/13)

PD 0332991 (Palbociclib) is a highly selective reversible inhibitor of CDK 4 and 6 currently being evaluated as an anti-cancer therapy.[33] Androgens drive proliferation of prostate cancer cells via up regulation of cyclin D which complexes with the kinase CDK4/6, resulting in phosphorylation of RB which in turn drives G1/S progression. Currently, the rates of RB loss or mutation (as measured by array CGH or exome capture) ranges between roughly 1-20% in localized prostate cancer (1% for 2 copy deletion versus 10-20% for 1 copy deletion)[34] to 30-40% in heavily treated metastatic castration-resistant prostate cancer[35]. The reported rates of loss of RB protein expression, by immunohistochemistry, range from 0% in prostatectomy series[36] to 40% in primary (TURP) tumor specimens in CRPC patients (unpublished data, Karen Knudsen, Thomas Jefferson University) to 70%

in metastases in CRPC patients.[37] Although, there is little data examining RB loss in the hormone sensitive metastatic population we aim to study here, by extrapolation of existing data, we hypothesize the rate to be between 10-20%.

We hypothesize that the addition of PD 0332991 to initial ADT in patients with newly metastatic RB-positive prostate cancer may significantly increase the efficacy of ADT. We postulate that similar to the Phase II trial of PD 0332991 in breast cancer, responses and survival could be predicated on retention of wild-type RB function. To assess this, we are conducting this randomized phase II study of PD 0332991 in which patients with newly diagnosed mHSPC and RB-expressing tumors based on metastatic disease biopsy will be randomized (1:2) to ADT or ADT plus PD 0332991. We propose to use confirmed PSA response (≤ 4 ng/mL) at 7 months of therapy as the primary endpoint because it is an intermediate endpoint that correlates significantly with overall survival in hormone-sensitive patients.{Hussain, 2006, Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162)[38];Hussain, 2009, Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916.[39]
Two other DOD-PCCTC participating sites are participating in this trial, Johns Hopkins University and the Dana-Faber Cancer Institute (Vanderbilt, Thomas Jefferson University and the University of Utah are also participating in this trial). The target accrual number is 60 patients. We are close to approval of Amendment 1 (FDA review protocol changes) and expect to activate this trial in June of 2014.

9. **c13-127, A Three Arm Randomized Open-Label Phase II Study of Radium-223 Dichloride 50kBq/kg and Versus 80 kBq/kg Versus 50 kBq/kg in an Extended Dosing Schedule in Subjects with Castration-Resistant Prostate Cancer Metastatic to the Bone.(LOI circulated 8/27/13)**
Alpharadin (Radium-223 dihydorchloride) was recently shown to improve survival in men with symptomatic bone metastases [40,41]. And approved by the FDA in the post-docetaxel setting. Subjects enrolled into the study will be randomized to one of the 3 treatment arms in 1:1:1 fashion: radium-223 dichloride 50 kBq/kg IV every 28 days for up to 6 doses (Treatment Arm A) or radium-223 dichloride 80 kBq/kg IV every 28 days for up to 6 doses (Treatment Arm B) or radium-223 dichloride 50 kBq/kg IV every 28 days for up to 12 doses (Treatment Arm C). The randomization will be permuted-block, stratified by use of prior chemotherapy (≤ 1 regimen versus > 1 regimen) and by total ALP (< 220 U/L versus ≥ 220 U/L). The primary objective of the study is to evaluate efficacy as measured by symptomatic skeletal event-free survival (SSE-FS) of radium-223 dichloride 50 kBq/kg every 28 days for up to 6 doses compared to radium-223 dichloride 80 kBq/kg every 28 days for up to 12 doses in subjects with castration resistant prostate cancer (CRPC) metastatic to bone symptomatic skeletal events (SSEs). The target accrual number for this study is 360 patients. Four other DOD-PCCTC member institutions are participating in this trial (OHSU,R-CINJ, WSU and U of C). We expect to activate this trial in July of 2014.

The following is the trial that was presented by University of Michigan to the consortium and accepted for consortium participation during our fifth year of participation, 2013-2014

10. **c14-135, A Phase Ib, Open-label, Dose-escalation Study of the Safety and Pharmacology Of GDC-0068 in Combination With Docetaxel, Fluoropyrimidine Plus Oxaliplatin, Paclitaxel, or Enzalutamide in Patients With Advanced Solid Tumors. (LOI circulated 2/26/14).**
GDC-0068 is a potent, novel, selective, ATP-competitive small molecule inhibitor of all three isoforms of the serine/threonine kinase Akt and has proven to be potent in nonclinical models including PTEN-null and PI3K-mutated tumors in vitro and in vivo. It inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, such as PRAS40, and the more downstream targets, such as S6RP, through inhibiting the activity of mTORC1, resulting in G1 arrest and/or apoptosis in human cancer cells.

Protocol PAM4983g has been amended to include an additional arm (Arm D) to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of GDC-0068 in combination with enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer. There is a strong preclinical rationale for cooperativity/ cross-talk between the androgen and Akt pathways. In preclinical xenograft models, enhanced combination effects of GDC-0068 and enzalutamide (relative to either agent alone) have been observed. Treatment in Arm D aims to evaluate the safety and tolerability of GDC-0068 in combination with enzalutamide, as well as to assess the pharmacokinetics and drug-drug interaction between GDC-0068 and enzalutamide.

At least 60% of metastatic prostate cancers have functional loss of PTEN.[42] PTEN loss has been associated with increased Akt phosphorylation, advanced disease, and Gleason stage, as well as a poor prognosis (Ayala et al. 2004).[43] These data provide a strong rationale for developing therapeutics to target the PI3K/Akt pathway in prostate cancer.

Recent nonclinical data suggest that the androgen receptor and Akt pathways cross-regulate one another through reciprocal feedback. Carver et al (2011)[44] showed that simultaneous pharmacologic inhibition of PI3K/mammalian target of rapamycin (mTOR) and androgen receptor cause near complete prostate cancer regression in PTEN-deficient prostate cancer models. In preclinical models, GDC-0068 when combined with an androgen receptor inhibitor enzalutamide (MDV3100) results in a more substantial tumor growth inhibition versus either agent alone (see GDC-0068 Investigator's Brochure for details). Therefore, combined inhibition of the androgen receptor and Akt pathways may result in improved clinical benefit in patients with prostate cancer.

Enzalutamide (MDV3100) was recently approved for the treatment of patients with metastatic CRPC who previously received docetaxel. Additionally, National Comprehensive Cancer Network (NCCN) Guidelines allow treatment with enzalutamide for symptomatic metastatic CRPC patients who are not candidates for docetaxel-based therapy.

Two other DOD-PCCTC member institutions are participating in this trial (UCSF and JHU) our site activated on 1/28/14 and has accrued two patients to the trial to date.

Please see Table A for a detailed description and the current status of these studies.

DOD-PCCTC participating institutions are charged with maintaining an annual accrual rate of 35 patients to DOD-PCCTC participating trials.

Currently, there are two DOD-PCCTC trials actively accruing (c11-089 and c14-135), two trials pending site activation (c13-123 and c13-127), and fourteen trials closed to accrual. The University of Michigan site has accrued 140 patients during this five year award period with 27 patients accrued during the fifth year of this award. This is an average of 28 patients per year. During this award period we accrued 19 patients to our phase II biomarker trial SWOG S0925 (b11-011) and 8 patients to the OGX-011 biomarker trial (b11-010) **(Table 4). Please refer to Table 2 for trial status information and Table 4 for the accrual numbers for the trials that accrued in this period.**

DOD-PCCTC participating institutions are charged with introducing at least one clinical trial to the consortium per year with the expectation of presenting two or more clinical trials to the consortium per year.

In this current 5 years reporting period, the University of Michigan site has introduced 10 trials to the consortium **(Table A)** which averages out to 2 trials per year.

DOD-PCCTC participating institutions are charged with accruing at least 5% of all accrued patients, independently or in partnership with other consortium or non-consortium institutions, will be from disproportionately affected populations.

(Table C and D) show that we have accrued approximately 9% of our accruals for this five reporting period from disproportionately affected populations (DAP).

DOD-PCCTC participating institutions are charged with patient contributions to trials from other sites shall constitute at least 20% of the total number of patients our site contributes to all trials.
(Table E) shows that our patient contribution to trials from other sites constituted 36% of the total number of patients our site contributed to all trials over this five year reporting period.

Table 4: Total and current reporting period University of Michigan Accruals to DOD-PCCTC Trials

DOD Number	PROTOCOL TITLE	UM PI	Total UM Accrual (Apr 01 2009-Mar 31 2014)	UM Accrual Apr 01 2013– Mar 31 2014
c07-012	A Phase II Study of AT101 to abrogate BCL-2 Mediated Resistance to Androgen Ablation Therapy in Patients with Newly Diagnosed Stage D2 Prostate Cancer	**Dr. Hussain**	16	0
c08-001	A Phase 2, Multicenter, Randomized Study of IMC-A12 or IMC-1121B Plus Mitoxantrone and Prednisone in Metastatic Androgen-Independent Prostate Cancer (AIPC) Following Disease Progression on Docetaxel-Based Chemotherapy	**Dr. Hussain**	7	0
c08-009	A Phase I/II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-Refractory Prostate Cancer (Study # CA301)	**Dr. Hussain**	12	0
c09-024	A Randomized, Phase II Study of GW786034 (Pazopanib) in Stage D0 Relapsed Androgen Sensitive Prostate Cancer Following Limited GnRH Agonist Therapy	**Dr. Hussain**	1	0
c09-031	A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temozolomide (an Oral DNAMethylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease.	**Dr. Hussain**	6	0
c09-033	A Randomized Phase II Clinical Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer	**Dr. Smith**	5	0
c09-057	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	**Dr. Hussain**	4	0
c09-044	A Phase 2 Multicenter Open-label Study Evaluating the Safety and Efficacy of TAK-700 in Patients with Nonmetastatic Castration-resistant Prostate Cancer (CRPC) and a Rising Prostate-specific Antigen (PSA)	**Dr. Hussain**	6	0
c10 -071	A Phase II study of single-agent tesetaxel in chemotherapy-naive and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer	**Dr. Hussain**	8	0
c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	**Dr. Smith**	29	0
c10-073	A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with the Combination of Cediranib (AZD2171) plus BMS-354825 (Dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer	**Dr. Smith**	3	0
c10-072	An Open-Label, Phase 1/2 Safety, Pharmacokinetic, and Proof-of-Concept Study of ARN-509 in Patients with Progressive Metastatic Castration-Resistant Prostate Cancer	**Dr. Smith**	1	0

c11-089	A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer: NCI 9012	**Dr. Hussain**	27	12
c12-111	A Phase 2, Open-label, Multicenter Study of PSMA ADC in Subjects with Castration-resistant Metastatic Prostate Cancer (CRMPC)	**Dr. Smith**	8	8
c12-104	An Open Label, Multicenter, Phase 2 Study to Determine the Safety and Efficacy of BIND-014 (Docetaxel Nanoparticles for Injectable Suspension), Administered to Patients With Metastatic Castration-Resistant Prostate Cancer	**Dr. Alva**	5	5
c14-135	A Phase Ib, Open Label, Dose Escalation Study of the Safety and Pharmacology of GDC 0068 in Combination with Docetaxel, Fluororpyrimidine plus Oxaliplatin, Paclitaxel, or Enzalutamide in Patients with Advanced Solid Tumors	**Dr. Hussain**	2	2
Totals			**140**	**27**

Biomarker Trials

DOD Number	PROTOCOL TITLE	UM PI	Total UM Accrual	UM Accrual Apr 01 2013– Mar 31 2014
b11-011	A Randomized Phase II Study of Combined Androgen Deprivation Versus Combined Androgen Deprivation with IMC-A12 for Patients with New Hormone Sensitive Metastatic Prostate Cancer (SWOG 0925)	**Dr. Hussain**	19	0
b11-010	A Randomized Phase 3 Study Comparing Standard First-Line Decetaxel/Prednisone to Decetaxel/Prednisone in Combination with Custirsen (OGX-011) In Men With Metastatic Castrate Resistant Prostate Cancer. (OGX-11-10)	**Dr. Smith**	8	0
Totals			**27**	**0**

KEY ACCOMPLISHMENTS

University of Michigan Comprehensive Cancer Center

As of April 1, 2014, our accomplishments during the five year award period are listed below.

Infastructure

• Collaborated with other DOD-PCCTC sites to improve the data collection process with the consortium database, to make the system more time effective and accurate.

• Participated in all the Prostate Cancer Clinical Trials Consortium meetings, including the most recent DOD-PCCTC PI/coordinator meeting at ASCO on May 31st in Chicago, Illinois, and the DOD-EAB annual review teleconference held February 28th, 2014 .

• Extended collaboration between the DOD-PCCTC and the University of Chicago CTEP-sponsored Phase II Consortium and other non-consortium sites.

Research/Protocol Development

•Introduced ten trials to date to the DOD-PCCTC consortium for the five years of the new award period (effective April 1, 2009) (see also **Table A. Trials Introduced by the University of Michigan**)

1. c09-031, ABT-888 – LOI circulated 2/25/2009
2. c09-044, TAK-700 – LOI circulated 7/9/2009
3. c09-057, EMD 525797 – LOI circulated 12/11/09 and 4/28/10
4. c11-079, XL184 – LOI circulated 1/5/11
5. c11-080, Everolimus – LOI circulated 2/10/11
6. c11-089, ABT-888/Abi/Gene Fusion – LOI circulated 8/10/11
7. c12-111, PSMA ADC – submitted to the PCCTC CC 11/2/12 – LOI circulated 3/13/13
8. c13-123, PD 0332991 (Palbociclib) - LOI circulated 6/17/13
9. c13-127, Radium-223 – LOI circulated 8/27/13
10. c14-135, GDC-0068 – LOI circulated 2//26/14

• Served as the lead site for the DOD-PCCTC for ten protocols to date for the five years of the new award period (effective April 1, 2009).

1. c09-031, ABT-888 – UM site activated 5/17/10
2. c09-044, TAK-700 – UM site activated 4/8/10
3. c09-057, EMD 525797 – UM site activated 6/9/11
4. c11-079, XL184 – UM site activated 12/7/09 (to DOD-PCCTC 1/5/11)
5. c11-089, ABT-888/Abi/Gene Fusion – UM site activated 4/18/12
6. c11-80, Everolimus – UM site activated 10/19/12
7. c12-111, PSMA ADC– UM site activated 3/28/12
8. c113-123, PD 0332991 (Palbociclib) – UM site pending activation (expected June 2014)
9. c13-127, Radium-223 – UM site pending activation (expected July 2014)
10. c14-135, GDC-0068, UM Site activated 1/28/14

•Completed fourteen protocols to date for the five years of the new award period (effective April 1, 2009). Three of these protocols completed during this reporting period (April 1, 2013 to March 31, 2014).

1. c07-012, AT-101- closed 9/14/10, terminated 12/13/11
2. c08-009, Nab-docetaxel – closed 10/20/09- re-opened 12/10/10- closed 1/31/11, terminated 1/8/14
3. c09-024, Pazopanib- closed 4/20/10, terminated 3/30/11
4. c09-031, ABT-888 – closed 10/22/10, terminated 12/13/11
5. c09-033, Itraconazole – closed 10/1/10, terminated 11/21/13
6. c09-044, TAK-700 – closed 6/17/11, terminated 2/19/13
7. c10-072, Cediranib/Dasatinib – on-hold to accrual 2/14/12- closed 7/31/12, permanently closed to accrual 12/31/12
8. c10-072, ARN-509, closed to accrual 5/21/12

9. c09-057, EMD Serono 525797- closed 10/23/12
10. c10-071, Tesetaxel – closed 8/3/12
11. c11-079, XL-184 RDT- closed 2/29/12
12. c12-104, BIND-014, - sponsor hold on enrollment11/6/13, 33 of 40 patient goal enrolled
13. c12-111, PSMA ADC 2301- closed 4/1/14, completed enrollment (35/35) to cytotoxic chemo-naïve arm
14. c11-080, Everolimus + Hormones and Radiation, closed 4/3/14, lack of funds

•Three of the DOD-PCCTC trials that were activated during for the five years of this award period were based on scientific data generated by our group.

1. c07-012, AT-101, trial was based on an agent that was developed by a University of Michigan scientist through work funded by our Prostate Cancer SPORE. The study design of the protocol was based on data published by Dr. Hussain regarding the relationship of PSA nadir after ADT with survival in new M1 patients. The trial completed accrual in 18 months and closed in September 2010.
2. c11-080, Everolimus, Dr. Daniel Hamstra wrote the protocol for this study, which was based on pre-clinical work supported by a Young Investigator Award from the PCF. Trial was activated on 10/19/2012.
3. c11-089, ABT-888/Abi/Gene Fusion- The TMPRSS2-ETS gene fusion was discovered by a University of Michigan researcher and the key biological data that provided the rational for the study also originated from our group. This trial was one of the lead trials of the recently awarded Stand Up To Cancer (SU2C) Grant that the University of Michigan is leading. This trial was activated at our site on 4/18/2012 and all twelve of the participating institutions have been activated. Twenty-seven of the 119 patients that were accrued to this study between 5/3/2012 and 3/31/2014 were from our site.

• Accrued 140 patients to DOD-PCCTC trials to date for the five years of the new award period (105 in the previous three year award period).
• Collected 2,481 samples for correlative studies of DOD-PCCTC trials at the end of the fifth year of the award period (with ~1,500 samples from the previous three year award period).

REPORTABLE OUTCOMES
University of Michigan Comprehensive Cancer Center

During the 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 22 abstracts and 13 manuscripts. 22 abstracts and 12 manuscripts have been published. A complete listing of abstracts and publications appears in **t**he **Bibliography** section, and the abstracts themselves appear in the **Appendix**.

Year 1 (01 Apr 2009- 31 Mar 2010)
During the 1st year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 1 abstract and 4 manuscripts. The abstract and all manuscripts have been published. A complete listing of abstracts and publications appears in References, and the abstract appears in the Appendix.

In this reporting period, during our first 12 months of funding, two studies have been completed. We published four manuscripts, one on the c05-009 study in the journal Cancer (see **Appendix W**) and one on the c05-010 study in the journal Investigational New Drugs (see **Appendix X**). Dr. Hussain was co-author on the c07-009 manuscript published in Investigational New Drugs (see **Appendix Y)** and Dr. Smith was a co-author on the c05-008 manuscript published in the Journal of Oncology (see **Appendix Z).**

During 2010, the following abstract was presented at the following ASCO meeting:
• c05-007,EMD 121974 in patients with nonmetastatic castration-resistant prostate cancer (CRPC) NCI-6735: A study by the DOD/PCF Prostate Cancer Clinical Trials Consortium. PI: Dr. Maha Hussain. 2010 ASCO GU Symposium. Abstract No. 152 (see **Appendix A)**

Year 2 (01 Apr 2010- 31 Mar 2011)
During the 2nd year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 5 abstracts, 1 poster presentation, 1 oral presentation and 2 manuscripts. The abstract and all manuscripts have been published. A complete listing of abstracts and publications appears in the Bibliography section, and the abstracts and manuscripts appear in the Appendix section.
In this reporting period, during our second 12 months of funding, five studies have been completed. We published one manuscript on the c05-007 study in the journal Investigational New Drugs (see **Appendix AA**). Dr. Smith was a co-author on the c05-008 manuscript published in the journal Cancer (see **Appendix BB)**.

c07-012 is a CTEP-sponsored Phase II trial evaluating AT-101 in men with new M1 prostate cancer. This trial was based on an agent that was developed by a University of Michigan scientist (Dr. Shaomeng Wang) through work funded by our Prostate Cancer SPORE. Pre-clinical data from our group led to moving this agent into the clinic. The study design of this trial is based on data published by Dr. Hussain regarding the relationship of PSA nadir after ADT with survival in new M1 patients. 20/55 patients accrued to this trial were from our center. This trial completed accrual in September, 2010.

During this reporting period, the following abstracts were presented at the following scientific meetings:

• c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting 2011. Author: Dr. Maha Hussain. Abstract PC080189-2043). **(Appendix B)**

• The Prostate Cancer Clinical Trials Consortium: A Collaborative Multicenter Prostate Cancer Research Model. Presentation at the Innovative Minds in Prostate Cancer Today. IMPaCT Meeting 2011 (Abstract PC081610-1865). Co-author: Dr. Maha Hussain. **(Appendix C**)

•c07-012- Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC). American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 137).Co-author: Dr. Maha Hussain. **(Appendix D)**

•c09-024 – A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 170). Co-author: Dr. Maha Hussain. **(Appendix E)**

•c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 127). Author: David C. Smith. **(Appendix F)**

•c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. Poster presentation at the 22nd EORTC-AACR Symposium on Molecular Targets and Cancer Therapeutics. 2010. Author: David C. Smith **(Appendix G)**

•c11-079- Cabozantinib (XL184) in metastatic castration resisitant prostate cancer (mCRPC): Results from a phase 2 randomized trial. Oral presentation submitted to the American Society of Clinical Oncology (ASCO) Annual Symposium, Genitourinary Cancer Session, 2011. Author: Dr. Maha Hussain **(Appendix H)**

Year 3 (01 Apr 2011- 31 Mar 2012)

During the 3nd year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 4 abstracts (c08-001, IMC A-12, IMC-1121B), (c09-031, ABT-888) (c09-033, Itraconazole) and (c09-044, TAK-700; 3 poster presentations (c08-001, c09-031 and c09-044); 1 oral presentation (c09-044), and 1 manuscript (c09-024). The abstract and all manuscripts have been published. A complete listing of abstracts and publications appears in the Bibliography section, and the abstracts and manuscripts appear in the Appendix section. In this reporting period, during our third 12 months of funding, two studies were closed (c09-044, TAK-700 on 6/17/11) having met the accrual goal and (c010-073, Cedirinib/Dasatinib) (on-hold to accrual as of 2/14/12, study to close by 7/31/12). Dr. Hussain was a co-author on the c09-024 (Pazopanib) manuscript in the journal Prostate Cancer and Prostatic Diseases (see **Appendix CC**).

During this reporting period, the following abstracts/posters were presented at the following scientific meetings:

c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC 1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 97). Author: Dr. Maha Hussain. **(Appendix I)**

c09-031 - Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 224). Author: Dr. Maha Hussain. **(Appendix J)**

c09-033 - A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial. American Society of

Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4532). Co-author: Dr. David C. Smith. **(Appendix K)**

c11-079 - Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4516). Author: Dr. Maha Hussain. Co-author: David C. Smith. **(Appendix L)**

c09-044 - Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study. Abstract and poster presented by Dr. Hussain at the 27th Annual Congress of the European Association of Urology (EAU). Paris, France. 2012. **(Appendix M)**

Year 4 (01 Apr 2012- 31 Mar 2013)

During the 4th year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 3 abstracts; 1 for (c11-079, XL184 RDT) (**Appendix N**), and 2 for (c09-044, TAK-700) (**Appendix O and P**); 2 poster presentations (c09-044) (**Appendix N and O**); 1 oral presentation (c11-079) (**Appendix N**) and 2 manuscripts (c11-079 and c09-033) (**Appendix DD and EE**). Results for the c09-044 (TAK-700) study were presented as a poster presentation at the 2013 ASCO Annual meeting May 31-June 4th in Chicago (see title below) and were presented at the 18th annual EAU Congress March 15th- March 19th 2013, in Milan, Italy (**Appendix P**). A complete listing of published abstracts and publications appears in the Bibliography section, and the abstracts and manuscripts appear in the Appendix section. In this reporting period, during our fourth 12 months of funding, five studies were closed (c09-079, EMD Serono, on 10/23/13 having met the accrual goal; c11-079 XL-184 on 2/29/12; c10-073, Cedirinib/Dasatinib, (on-hold to accrual as of 2/14/12, study to close by 7/31/2012) and c10-071, Tesetaxel, as of 8/3/12, sponsor (Genta) declared bankruptcy and c10-072, ARN-509, closed to accrual 5/21/12, enrollment goal was met. Dr. Smith was first author on a manuscript reporting the results from the PCCTC trial c11-079 (**Appendix DD)**. Dr. Smith was a co-author on the c09-033 (Itraconazole) manuscript in the journal The Oncologist (see **Appendix EE)**.

During this reporting period, the following abstracts/posters were presented or accepted at the following scientific meetings

- c11-079- Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE). American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session, 2012, J Clin Oncol 30:2012 (suppl: abstr 4513). **Co-authors: Dr. David C. Smith and Maha Hussain (Appendix N)**
- c09-044- Safety and activity of the investigational agent orteronel (ortl) without prednisone in men with nonmetastatic castration-resistant prostate cancer (nmCRPC) and rising prostate-specific antigen (PSA): Updated results of a phase II study. American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session, 2012, J Clin Oncol 30:2012 (suppl: abstr 4549). **Senior author: Maha Hussain (Appendix O).**
- 09-044- A phase 2 multicenter study of the investigational single agent orteronel (TAK-700) in nonmetastatic castration-resistant prostate cancer (nmCRPC) and rising prostate-specific antigen (PSA). Abstract and poster presented by Susan Moran Arangio at the 28th Annual Congress of the European Association of Urology (EAU). Milan, Italy. 2013 (abstract and poster #100). **First Author: Maha Hussain (Appendix P).**
- c09-044- Safety, efficacy, and health-related quality of life (HRQoL) of the investigational single agent orteronel (ortl) in nonmetastatic castration-resistant prostate cancer (nmCRPC). Poster presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, 2013,J Clin Oncol 31, 2013 (suppl; abstr 5076). **First author: Maha Hussain (Appendix Q)**

During this reporting period, the following manuscripts were published in the following scientific journals:

- c11-079**-** Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. J Clin Oncol Vol 31 No 4 Feb 1 2013, 412-419. **First Author: David C. Smith. Senior Author: Maha Hussain. (Appendix DD)**
- c09-033**-** Repurposing Itraconazole as a Treatment for Advanced Prostate Cancer: A Noncomparative Randomized Phase II Trial in Men With Metastatic Castration-Resistant Prostate Cancer. The Oncologist 2013; 18:163-173 **David C. Smith: Co-author. (Appendix EE)**

Year 5 (01 Apr 2013- 31 Mar 2014)

During the 5th year of this 5-year grant period, investigators at the University of Michigan have been listed as authors on a total of 5 abstracts, 2 each for c12-111, PSMA ADC 2301 **(Appendix R and T)** and c11-089, Gene Fusion, (**Appendix S and V**) and 1 for c09-057, EMD 525797 **(Appendix U)**, 1 poster presentation, c12-111 **(Appendix R)** and 4 manuscripts (c09-031 ABT-888, c09-044 TAK-700, c11-079 XL184 and c10-073 Cediranib/Dasatinib,) **(Appendix-HH).** A complete listing of published abstracts and publications appears in the Bibliography section, and the abstracts and manuscripts appear in the Appendix section.

In this reporting period, during our fourth 12 months of funding, three studies were closed, (c12-104, BIND-014 on 11/6/13, close to enrollment goal (33/40 patients enrolled), c12-111, PSMA ADC 2301 on 4/1/14 having met the enrollment goal (35/35 patients on the cytotoxic chemo-naïve treatment arm) and c11-080, Everolimus, closed on 4/3/14 due to lack of continued funding.
During this reporting period, the following abstracts/posters were presented or accepted at the following scientific meetings

- **c12-111- A phase II trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC)**. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, 2014, General Poster Session A: Prostate Cancer, J Clin Oncol 32, 2014 (suppl 4; abstr 83). **David C. Smith**, **Co-author**. **(Appendix R)**

- **c11-089, Concordance of ETS fusion status of matched metastatic castration-resistant prostate cancer and primary prostate cancer: Data from NCI 9012, a randomized ETS fusion-stratified phase II trial.** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the American Society of Clinical
- Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No. 5219. **M. Hussain: Co-author. (Appendix S)**

- **c12-111**, **A phase 2 trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC).** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5023**. **David C. Smith**, **Co-author. (Appendix T)**

- **c09-057- Primary outcomes of the placebo-controlled phase 2 study PERSEUS (NCT01360840) investigating two dose regimens of abituzumab (DI17E6, EMD 525797) in the treatment of chemotherapy-naive patients (pts) with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC).** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5030**. **Maha Hussain: First Author. (Appendix U)**

- **Comprehensive molecular profiling of pretreatment metastatic castration resistant prostate cancer (CRPC): Secondary data from NCI 9012, a randomized ETS fusion-stratified phase II trial. Maha Hussain: Senior Author.** Accepted as a publication-only abstract published in conjunction with the 2014 ASCO Annual Meeting **but not presented at the Meeting**, can be found online only. **Abstract No. e16038**. **(Appendix V).**

During this reporting period, the following manuscripts were published/accepted for publication in the following scientific journals

- **c09-031-Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer. *Invest New Drugs,* 26 April 2014 [Epub ahead of print]. PMID: 24764124. Maha Hussain: First Author. (Appendix FF)**

- **c09-044- Phase II Study of Single Agent Orteronel (TAK-700) in Patients with NonmetastaticCastration-Resistant Prostate Cancer and Rising Prostate-Specific Antigen.**. Submitted to ***Clinical Cancer Research***, 05 May 2014, awaiting final decision**. Maha Hussain: First Author.**

- **c11-079, Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort**. ***European Urology*, Epub ahead of print, 20Feb2014. PMID: 24631409. David C. Smith: Co-author. (Appendix GG)**

- **c10-073, A randomized phase II study of cediranib alone versus cediranib in combination with dasatinib in docetaxel resistant, castration resistant prostate cancer patients**. ***Invest New Drugs*, Epub ahead of print, 03May2014.PMID: 24788563. David C. Smith: Co-author. (Appendix HH**)

CONCLUSIONS

University of Michigan Comprehensive Cancer Center

The contributions and participation of the University of Michigan during this reporting period (04-01-2009 to 03-31-2014) of the DOD-PCCTC CCA research site award are summarized in this report.

The focus of the University of Michigan during the this period of the DOD-PCCTC has been to work with consortium investigators and outside sponsors to bring novel research to the DOD-PCCTC, to actively accrue to DOD PCCTC trials, and to expand collaboration with other non-consortium institutions.

University of Michigan research personnel have actively participated in a variety of activities to facilitate research and communication between participating institutions including teleconferences, scheduled conference calls and Investigator meetings.

The University of Michigan has presented a total of ten studies to the DOD-PCCTC for member participation since April 2009 (see study list in Key Accomplishments section, Research/Protocol Development).

Currently, there are two DOD-PCCTC trials actively accruing at the University of Michigan (c11-089, ABT-888/Abi/Gene fusion) and (c14-135, GDC-0068) with two additional studies (c13-123, PD 0332991) and (c13-127, Radium-223) that we hope to activate in June and July 2014, respectively.

We have accrued 140 patients to DOD-PCCTC trials to date at the end of this fifth year of the new award (27 during this reporting period, with 15% accrued from disproportionately affected populations). Over the 5-year award period we have accrued 9% of patients from disproportionately affected populations.

We have activated one new consortium trial- during this reporting period.

1. c14-135, GDC-0068 – activated 1/28/14
   and expect to activate two other consortium trials (c13-123 (PD 0332991) and (c13-127, Radium-223) in June and July of 2014, respectively.

Our efforts have led to several national presentations and publications.

In addition to improving therapy our trials have a variety of embedded correlatives aimed at better understanding mechanisms of response and progression.

To date, we have collected approximately 2,481 samples (with ~1,500 samples from the previous three year award period) for the correlative endpoints to DOD-PCCTC trials.

In the 5 th year of this new funding period with the DOD-PCCTC, the University of Michigan will continue accrual to active consortium trials, will introduce new concepts that will capitalize on the scientific productivity of our group coupled with the accrual and scientific strength of the DOD-PCCTC, open additional consortium trials and continue to finalize analysis and reporting of completed projects

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Year 1 (01 Apr 2009 – 31 Mar 2010)

Abstracts:

A. c05-007 – EMD 121974 in patients with nonmetastatic castration-resistant prostate cancer (CRPC) NCI-6735: A study by the DOD/PCF Prostate Cancer Clinical Trials Consortium. A. S. Alva, S. F. Slovin, **S. Daignault**, M. A. Carducci, R. S. DiPaola, D. B. Agus, A. P. Chen, **M. Hussain. Presentation at the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, 2010. (Abstract#152)**

Year 2 (01 Apr 2010 – 31 Mar 2011)

B. c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy. **Maha Hussain**, Dana Rathkopf, Glenn Liu, Andrew J. Armstrong, William Kevin Kelly, Anna Ferrari, John Hainsworth, Ling Yang, Jonathan Schwartz, Hagop Youssoufian, Celestia S. Higano. **Innovative Minds in Prostate Cancer Today (IMPaCT) Meeting 2011 (Abstract PC080189-2043).**

C. Title: The Prostate Cancer Clinical Trials Consortium: A Collaborative Multicenter Prostate Cancer Research Model. **Presentation at the Innovative Minds in Prostate Cancer Today.** Howard I. Scher, Tomasz M. Beer, Michael A. Carducci, Paul Corn, Robert Dipaola, Daniel J. George, Andrea L. Harzstark, Elisabeth I. Heath, Celestia S. Higano, **Maha Hussain**, Michael J. Morris, Susan F. Slovin, Walter Stadler, Mary-Ellen Taplin, George Wilding. **(IMPaCT) Meeting 2011 (Abstract PC081610-1865).**

D. c07-012- Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC). M.N. Stein, I. Khan, **M. Hussain**, G. Lui, G. Wilding, E.M. Posadas, W.M. Stadler, C. Jeyamohan, S. Eddy, R.S. DiPaola, Prostate Cancer Clinical Trials Consortium. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 137).**

E. c09-024 – A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study. J.E.Ward, S. Limvorask, T. Karrison, G.S. Chatta, **M. Hussain**, D. H. Shervin, R.Z. Szmulewitz, W.M. Stadler, E. M. Posadas**. American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 170).**

F. c11-079 – Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. D.C. Smith, M.R. Smith, E.J. Small, C. Sweeney, R. Kurzrock, M.S. Gordon, N.J. Vogelzang, C. Scheffold, M.D. Ballinger, **M. Hussain**. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2011. J Clin Oncol 29:2011 (suppl 7: abstr 127).**

G. c11-079 -Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease. D.C. Smith, A. Spira, J. De Grève, L. Hart, S. Holbrechts, C.C. Lin, **M. Hussain**, S. Herrick, K. Houggy, N. Vogelzang. **Poster presentation at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, 2010.**

H. **c11-079- Cabozantinib (XL184) in metastatic castration resisitant prostate cancer (mCRPC): Results from a phase 2 randomized trial. M. Hussain,** M.R. Smith, C. Sweeney, P.G. Corn, A. Elfiky, M.S. Gordon, N. B. Haas, A.L. Harzstark, R. Kurzrock, P. Laura Jr., C. Lin, A. Sella, E.J. Small, A.I. Spira, U. N. Vaishampayan, N.J. Vogelzang, C. Scheffold, M.D. Ballinger, F. Schimmoller, **D.C. Smith**. **Oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, Genitourinary Cancer Session (Prostate Cancer), 2011.**

Year 3 (01 Apr 2011 – 31 Mar 2012)

I. **c08-001 – A phase 2 randomized study of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in patients (pts) with metastatic castration resistant prostate cancer (CRPC) following disease progression on docetaxel-based chemotherapy.** **Maha Hussain**, Dana Rathkopf, Glenn Liu, Andrew J. Armstrong, William Kevin Kelly, Anna Ferrari, John Hainsworth, Ling Yang, Jonathan Schwartz, Hagop Youssoufian, Celestia S. Higano. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 97).**

J. **c09-031 - Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Maha Hussain**, Michael Anthony Carducci, Susan F. Slovin, Jeremy Paul Cetnar, Jiang Qian, Evelyn Mary McKeegan, Elizabeth Litvinovich, Brenda Chyla, Robert Hetman, Bhardwaj Desai, Vincent L. Giranda, Joshi J. Alumkal. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, General Poster Session B (Prostate Cancer), 2012. J Clin Oncol 30:2012 (suppl 5: abstr 224).**

K. **c09-033 - A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial.** . S. Antonarakis, E. I. Heath, **D. C. Smith**, D. E. Rathkopf, A. L. Blackford, D. C. Danila, S. King, A. Frost, M. A. Carducci. **American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4532). UMICH - co-author.**

L. **c11-079 - Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. M. Hussain,** M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara, C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, D. C. Smith**. American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session Genitourinary (Prostate) Cancer, 2011. J Clin Oncol 29:2011 (suppl: abstr 4516).**

M. **c09-044 - Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study. Hussain, M.**, Corn, P., Michaelson, D., Hammers, H., Alumkal, J., Ryan, C., Bruce, J., Moran, S., Mortimer, P., Lee, S.Y., George, D. Abstract and poster presented by Dr. Hussain at the **27th Annual Congress of the European Association of Urology (EAU). Paris, France. 2012 (abstract and poster #124).**

Year 4 (01 Apr 2012 – 31 Mar 2013)

N. **c11-079- Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE)**. Matthew Raymond Smith, Christopher Sweeney, Dana E. Rathkopf, Howard I. Scher, Christopher Logothetis, Daniel J. George, Celestia S. Higano, Evan Y. Yu, Andrea Lynne Harzstark, Eric Jay Small, A. Oliver Sartor, Michael S. Gordon, Nicholas J. Vogelzang, **David C. Smith**, **Maha Hussain**, Johann

Sebastian De Bono, Naomi B. Haas, Christian Scheffold, Yihua Lee, Paul G. Corn;**American Society of Clinical Oncology (ASCO) Annual Meeting, Oral Abstract Session, 2012, J Clin Oncol 30:2012 (suppl: abstr 4513).**

O. c09-044- Safety and activity of the investigational agent orteronel (ortl) without prednisone in men with nonmetastatic castration-resistant prostate cancer (nmCRPC) and rising prostate-specific antigen (PSA): Updated results of a phase II study. Daniel J. George, Paul G. Corn, M. Dror Michaelson, Hans J. Hammers, Joshi J. Alumkal, Charles J. Ryan, Justine Yang Bruce, Susan Moran, Shih-Yuan Lee, Peter Mortimer, Maha Hussain; **American Society of Clinical Oncology (ASCO) Annual Meeting, Poster Discussion Session, 2012, J Clin Oncol 30:2012 (suppl: abstr 4549).**

P. c09-044 – A Phase 2 multicenter study of the investigational single agent orteronel (TAK-700) in nonmetastatic castration resisistant prostate cancer (nmCRPC) and rising prostate-specific antigen. Maha H. Hussain, Paul G. Corn, Dror Michaelson, Hans J. Hammers, Joshi J. Alumki, Charles J. Ryan, Justine Y. Bruce, Susan Moran, Peter Mortimer, Shih-Yuan Lee and Daniel. J. George. Abstract and poster presented by Susan Moran Arangio at the **28th Annual Congress of the European Association of Urology (EAU). Milan, Italy. 2013 (abstract and poster #100).**

Q. 09-044- Safety, efficacy, and health-related quality of life (HRQoL) of the investigational single agent orteronel (ortl) in nonmetastatic castration-resistant prostate cancer (nmCRPC): Updated results. Maha Hussain, Paul G. Corn, Dror Michaelson, Hans J. Hammers, Joshi J. Alumkal, Charles J. Ryan, Justine Y. Bruce, Susan Moran, David MacLean, Shih-Yuan Lee, H Mark Lin, Hongliang Shi, Yanyan Zhu, Peter Mortimer, and Daniel J. George**. Accepted for poster presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, 2013, May 31 to June 4, Chicago, Illinois.**

Year 5 (01 Apr 2013 – 31 Mar 2014)

R. c12-111- A phase II trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC). Daniel Peter Petrylak, **David C. Smith**, Leonard Joseph Appleman, Mark T. Fleming, Arif Hussain, Robert Dreicer, A. Oliver Sartor, Neal D. Shore, Nicholas J. Vogelzang, Hagop Youssoufian, William C. Olson, Nancy Stambler, Kathleen Huang, Robert Joseph Israel. **American Society of Clinical Oncology (ASCO) GU Cancers Symposium, 2014, General Poster Session A: Prostate Cancer, J Clin Oncol 32, 2014 (suppl 4; abstr 83).**

S. c11-089, Concordance of ETS fusion status of matched metastatic castration-resistant prostate cancer and primary prostate cancer: Data from NCI 9012, a randomized ETS fusion-stratified phase II trial.): L. P. Kunju, N. Palanisamy, S. Daignault, R. Mehra, J. Siddiqui, S. L. Carskadon**,** P. Twardowski, M. N. Stein, N. M. Hahn, W. M. Stadler, **J. Jacobson, M. S. Davenport, S. A. Tomlins, A. M. Chinnaiyan, F. Y. Feng, M. Hussain.** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5019**.

T. c12-111- A phase 2 trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC). Daniel Peter Petrylak, **David C. Smith**, Leonard Joseph Appleman, Mark T. Fleming, Arif Hussain, Robert Dreicer, A. Oliver Sartor, Neal D. Shore, Nicholas J. Vogelzang, Hagop Youssoufian, Vincent A. DiPippo, Nancy Stambler, Kathleen Huang, Robert Joseph Israel. Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5023**.

U. **c09-057- Primary outcomes of the placebo-controlled phase 2 study PERSEUS (NCT01360840) investigating two dose regimens of abituzumab (DI17E6, EMD 525797) in the treatment of chemotherapy-naive patients (pts) with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC). Maha Hussain,** Kurt Miller, Ilona Rybicka, Rolf Bruns**.** Accepted as part of the Poster Highlights Session: Genitourinary (Prostate) Cancer at the **American Society of Clinical Oncology (ASCO) Annual Meeting, 2014, May 30 to June 3, Chicago, Illinois. Abstract No: 5030**.

V. **Comprehensive molecular profiling of pretreatment metastatic castration resistant prostate cancer (CRPC): Secondary data from NCI 9012, a randomized ETS fusion-stratified phase II trial.** Scott A. Tomlins, Dan Robinson, Yi-Mi Wu, Robert J Lonigro, Pankaj Vats, Shanker Kalyana Sundaram, Xuhong Cao, Lakshmi Priya Kunju, Nallasivam Palanisamy, Stephanie Daignault, Rohit Mehra, Javed Siddiqui, Arul M. Chinnaiyan, Felix Yi-Chung Feng, Maha Hussain**.** Accepted as a pubication-only abstract published in conjunction with the 2014 ASCO Annual Meeting **but not presented at the Meeting**, can be found online only. **Abstract No. e16038**.

Publications

Year 1 (01 Apr 2009 – 31 Mar 2010)

W. **c05-009 – Vorinostat in Advanced Prostate Cancer Patients Progressing on Prior Chemotherapy (National Cancer Institute Trial 6862): Trial Results and Interleukin-6 analysis: A study by the Department of Defense Prostate Cancer Clinical Trial Consortium and University of Chicago Phase 2 Consortium. Deborah Bradley**, Dana Rathkopf; **Rodney Dunn**, Walter M. Stadler, Glenn Liu, **David C. Smith**, Roberto Pili, James Zwiebel, Howard Scher, and **Maha Hussain**. ***Cancer*. 2009 Dec 1 2009; 115 (23) 5541-9.**

X. **c05-010 – Cilengitide (EMD 121974, NSC 707544) in asymptomatic metastatic castration resistant prostate cancer patients: a randomized phase II trial by the prostate cancer clinical trials consortium. Deborah A. Bradley, Stephanie Daignault,** Charles J. Ryan, Robert S. DiPaola **, David C. Smith,** Eric Small, Mitchell E. Gross, Mark N. Stein, Alice Chen, **Maha Hussain.** ***Invest New Drugs* 2011 Dec;29(6):1432-40. Epub 2010 PMCID: PMC2917503**

Y. **c07-009 – Oral enzastaurin in prostate cancer : A two cohort phase II trial in patients with PSA progression in the non-metastatic castrate state and following docetaxel-based therapy.** Robert Dreicer, Jorge Garcia, **Maha Hussain**, Brian Rini, Nicholas Vogelzang, Sandy Srinivas, Bradley Somer, Yan D. Zhao, Marek Kania, Derek Raghavan ***Invest New Drugs* 2011 Dec;29(6):1441-8. Epub 2010 Arp 6. PMID: 20369375**

Z. **c05-008 - Phase I Study of Ixabepilone, Mitoxantrone, and Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Therapy: A Study of the Department of Defense Prostate Cancer Clinical Trials Consortium**. Jonathan E. Rosenberg, Charles J. Ryan, Vivian K. Weinberg, **David C. Smith**, **Maha Hussain**, Tomasz M. Beer, Christopher W. Ryan, Paul Mathew, Lance C. Pagliaro, Andrea L. Harzstark, Jeremy Sharib, and Eric J. Small. ***Journal of Clinical Oncology* Jun 2009: 2772–2778. PMCID: PMC2698016**

Year 2 (01 Apr 2010 – 31 Mar 2011)

AA. **c05-007 - Phase II study of Cilengitide (EMD 121974, NSC 707544) in patients with non-metastatic castration resistant prostate cancer, NCI-6735. A study by the DOD/PCF prostate**

cancer clinical trials consortium; Alva, A, Slovin S, Carducci M, Dipaola R, **Pienta K**, Agus D, **Cooney K**, Chen, A, **Smith DC, Hussain M**. ***Invest New Drugs*. 2012 Apr;30(2):749-57. Epub 2010 Nov 4. [PMCID: PMC3175265**

BB. c05-008 – Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy. A Phase 2 Study of the Department of Defense Prostate Clinical Trials Consortium; Harzstark AL, Rosenberg JE, Weinberg VK, Sharib J, Ryan CJ, **Smith DC**, Pagliaro LC, Beer TM, Liu G, Small EJ. ***Cancer* 2011 Jun 1;117(11):2419-25, Epub 2010 Dec 29. PMID: 21192058**

Year 3 (01 Apr 2011 – 31 Mar 2012)

CC. c09-024 - A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: a University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study. JE Ward, T Karrison, G Chatta, **M Hussain**, D Shevrin, RZ Szmulewitz, PH O'Donnell, WM Stadler and EM Posadas. ***Prostate Cancer and Prostatic Diseases* (2012) 15, 87–92. PMID: 22006050**

Year 4 (01 Apr 2012 – 31 Mar 2012)

DD. c11-079- Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial. David C. Smith, Matthew R. Smith, Christopher Sweeney, Aymen A. Elfiky, Christopher Logothetis,Paul G. Corn, Nicholas J. Vogelzang, Eric J. Small, Andrea L. Harzstark, Michael S. Gordon,Ulka N. Vaishampayan, Naomi B. Haas, Alexander I. Spira, Primo N. Lara Jr, Chia-Chi Lin, Sandy Srinivas,Avishay Sella, Patrick Schöffski, Christian Scheffold, Aaron L. Weitzman, and **Maha Hussain**. ***J Clin Oncol* Vol 31 No 4 Feb 1 2013, 412-419. PMID: 23169517.**

EE. c09-033- Repurposing Itraconazole as a Treatment for Advanced Prostate Cancer: A Noncomparative Randomized Phase II Trial in Men With Metastatic Castration-Resistant Prostate Cancer. Emmanuel S. Antonarakisa, Elisabeth I. Heath **David C. Smith**, Dana Rathkopf, Amanda L. Blackford, Daniel C. Danila, Serina King, Anja Frost, A. Seun Ajiboye, Ming Zhao, Janet Mendonca, Sushant K. Kachhap, Michelle A. Rudek and Michael A. Carducci. ***The Oncologist* 2013; 18:163-173. PMCID: PMC3579600**

Year 5 (01 Apr 2013 – 31 Mar 2014)

FF. c09-031-Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer. Maha Hussain, Michael A. Carducci, Susan Slovin, Jeremy Cetnar, Jiang Qian,Evelyn M. McKeegan, Marion Refici-Buhr, Brenda Chyla, Stacie P. Shepherd, Vincent L. Giranda, Joshi J. Alumkal. ***Invest New Drugs,* 26 April 2014 [Epub ahead of print]. PMID: 24764124**

c09-044- Phase II Study of Single Agent Orteronel (TAK-700) in Patients with Nonmetastatic Castration-Resistant Prostate Cancer and Rising Prostate-Specific Antigen. Maha Hussain, Paul G. Corn, M. Dror Michaelson, Hans J. Hammers, Joshi J. Alumkal, Charles J. Ryan, Justine Y. Bruce, Susan Moran,, Shih-Yuan Lee, H. Mark Lin, Daniel J George, and Dr. Hussain for the Members of the Prostate Cancer Clinical Trials Consortium, a program of the Department of Defense Prostate Cancer Research Program and the Prostate Cancer Foundation. Submitted to ***Clinical Cancer Research***, 05 May 2014, awaiting final decision.

GG. c11-079, Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. Ethan M. Basch, Karen A. Autio, Matthew R. Smith, Antonia V. Bennett, Aaron L. Weitzman, Christian

Scheffold, Christopher Sweeney, Dana E. Rathkopf, **David C. Smith**, Daniel J. George, Celestia S. Higano, Andrea L. Harzstark, A. Oliver Sartor, Michael S. Gordon, Nicholas J. Vogelzang, Johann S. de Bono, Naomi B. Haas, Paul G. Corn, Frauke Schimmoller, Howard I. Scher. ***European Urology*, Epub, 20Feb2014. PMID: 24631409**

HH. c10-073, A randomized phase II study of cediranib alone versus cediranib in combination with dasatinib in docetaxel resistant, castration resistant prostate cancer patients. Anna Spreafico, Kim N. Chi, Srikala S. Sridha, **David C. Smith**, Michael A. Carducci, Peter Kavsak, Tracy S. Wong, Lisa Wang, S. Percy Ivy, Som Dave Mukherjee, Christian K. Kollmannsberger, Mahadeo A. Sukhai, Naoko Takebe, Suzanne Kamel-Reid, Lillian L. Siu, Sebastien J. Hotte. ***Invest New Drugs*, Epub, 03May2014. PMID: 24788563**

SUPPORTING DATA
University of Michigan

Table A. Trials Introduced by the *University of Michigan* (as of 04/01/2014)

LOI #	Protocol Title (Phase, Intervention, Population)	Target Accrual	Current Accrual (UM/ Other Sites)	Submitted		PI	PCCTC-DOD Participating Sites	Outcomes
				Start Date	End Date			
c09-031	A Phase II Trial of Combination ABT-888 (an Oral PARP Inhibitor) with Temozolomide (an Oral DNA Methylating Agent) in Patients progressing on up to Two Prior systemic Therapies for Castration Resistant Disease	25	26(6/20)	5/17/2010	10/22/10	Dr. Maha Hussain	MSK, OHSU, UCSF, UWisc	Met accrual goal.
c09-044	A Phase II Multicenter Open Label Study Evaluating TAK-700 in Patients with Nonmetastatic Castration Resistant Prostate Cancer and a Rising PSA	42	33(6/27)	4/8/2010	6/17/11	Dr. Maha Hussain	DF-HCC, OHSU, JHU, UCSF, MDACC, UWisc, Duke	Closed by Millennium due to difficulty in finding suitable patients
c09-057	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	165	165(4/161)	6/09/2011	10/23/12	Dr. Maha Hussain	MDACC, R-CINJ, Wayne State, UChicago	Met accrual goal.

c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	370	309(30/279)	12/17/09 1/5/11 to PCCTC	2/29/12	Dr. David Smith	MSK, DF-HCC, UCSF, MDACC, Wash, Duke, Wayne State	Closed by Millennium to minimize the overlap in study population in Phase III XL-184-306 study in prostate cancer.
c11-080	A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer	40	1/(0/1)	10/19/12	4/3/14	Dr. Daniel Hamstra	JHU	Closed by PI due to lack of continued funding.
c11-089	A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer: NCI 9012	148	119(27/92)	4/18/12		Dr. Maha Hussain	JHU, MDACC, R-CINJ, UChicago	
c12-111	PSMA ADC 2301 / A Phase 2, open-label, multicenter study of PSMA ADC in subjects with castration-resistant metastatic prostate cancer (CRMPC).	110	105(8/103)	4/02/13		Dr. David Smith	JHU	Met accrual goal.
c13-123	A Randomized Phase II Study of Androgen Deprivation Therapy with or without PD 0332991 in RB-Positive Metastatic Hormone-	60				Dr. Maha Hussain	DF_HCC, JHU	

	Sensitive Prostate Cancer							
c13-127	A three arm randomized open-label Phase II study of radium-223 dichloride 50 kBq/kg versus 80 kBq/kg, and versus 50 kBq/kg in an extended dosing schedule in subjects with castration-resistant prostate cancer metastatic to the bone	360				Dr. Maha Hussain	OHSU, R-CINJ	
c14-135	A Phase Ib, Open Label, Dose Escalation Study of the Safety and Pharmacology of GDC 0068 in Combination with Docetaxel, Fluororpyrimidine plus Oxaliplatin, Paclitaxel, or Enzalutamide in Patients with Advanced Solid Tumors	120	2(2/0)	1/28/14		Dr. Maha Hussain	JHU	

Table B. Trials in Which the *University of Michigan* Participated (as of 04/01/2014)

LOI #	Protocol Title (Phase, Intervention, Population)	Target Accrual	Current Accrual (UM/Other Sites)	Submitted		University of Michigan PI	Lead Site	Other Participating Sites
				Start Date	End Date			
c05-008	NCI 7347: Phase I/II trial of Epothilone Analog BMS-247550 (Ixabepilone), Mitoxantrone, and Prednisone in Hormone Refractory Prostate Cancer Patients Previously Treated with Chemotherapy	94	94(18/76)	6/1/2006	4/3/2009	Dr. David Smith	UCSF	OHSU MD Anderson
c07-012	A Phase II study of AT101, to abrogate bcl-2 mediated resistance to androgen ablation therapy in patients with newly diagnosed stage D2 prostate cancer: NCI 8014	55	55(20/35)	11/14/2008	9/14/2010	Dr. Maha Hussain	UWisc	CINJ, Univ of Chicago
c08-009	A Phase II Trial of ABI-008 (nab-docetaxel) in Patients with Hormone-refractory Prostate Cancer	35	28(12/16)	1/09/2009	10/27/2009	Dr. Maha Hussain	MDACC	
c09-024	A Randomized, Phase II Study of GW786034 (Pazopanib) in Stage D0 Relapsed Androgen Sensitive Prostate Cancer Following Limited GnRH Agonist Therapy	94	45(6/39)	11/1/2007	4/20/2010	Dr. Maha Hussain	UMich	UWisc, UChicago
c09-033	A Randomized Phase II Clinical Trial of Two Dose-Levels of Itraconazole in Patients with Metastatic Castration-Resistant Prostate Cancer	58	26(5/21)	12/1/2009	10/1/2010	Dr. David Smith	JHU	Wayne State

c09-044	A Phase 2 Multicenter Open-label Study Evaluating the Safety and Efficacy of TAK-700 in Patients with Nonmetastatic Castration-resistant Prostate Cancer (CRPC) and a Rising Prostate-specific Antigen (PSA)	42	33(6/27)	4/8/2010	6/17/11	Dr. Maha Hussain	UMICH	DF-HCC, OHSU, JHU, UCSF, MDACC, UWisc, Duke
c09-057	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Investigating Two Doses of EMD 525797 in Subjects with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (mCRPC)	165	165(4/161)	6/09/2011	10/23/12	Dr. Maha Hussain	UMICH	MDACC, CINJ, Wayne State, UChicago
c10-071	A Phase II study of single-agent tesetaxel in chemotherapy-naive and chemotherapy-exposed patients who have progressive, castration-resistant prostate cancer	57	26(8/18)	10/21/2011	8/3/12	Dr. Maha Hussain	MSKCC	UCSF, UWisc, CINJ
c11-079	A Randomized Discontinuation Study of XL184 in Subjects with Advanced Solid Tumors	370	309(29/280)	12/17/09 1/5/11 open to PCCTC	2/29/12	Dr. David Smith	UMICH	MSKCC, DF-CI, UCSF, MDACC, Wash, Duke, Wayne State
c10-073	A Phase 2 Randomized Study of Cediranib (AZD2171) Alone Compared with the Combination of Cediranib (AZD2171) plus BMS-354825 (Dasatinib, Sprycel) in Docetaxel Resistant, Castration Resistant Prostate Cancer	50	11(3/8)	10/20/2011	7/31/12	Dr. David Smith	JHU	

c11-080	A Multi-institutional Phase I and Biomarker Study of Everolimus Added to Combined Hormonal and Radiation Therapy for High Risk Prostate Cancer	40	1(0/1)	10/19/2012	Closed to accrual 4/3/14.	Dr. Daniel Hamstra	UMICH	Georgetown
c11-089	A Randomized Gene Fusion Stratified Phase 2 Trial Of Abiraterone With Or Without ABT-888 For Patients With Metastatic Castration-Resistant Prostate Cancer: NCI 9012	148	119(27/92)	4/18/12	Open and accruing	Dr. Maha Hussain	UMICH	JHU, UWisc, UWash, MDACC, CINJ, UChicago, City of Hope, U of North Carolina, Indiana Univ., NorthShore Univ.

Table C. Quarterly Patient Accrual by the *University of Michigan* (as of 04/01/2014)

Quarter	Accrual Per Quarter	DAP Accrual Per Quarter	Total Accrual To Date
2Q09	7	1	8
3Q09	10	1	19
4Q09	7		26
1Q10	10		36
2Q10	13	2	51
3Q10	10	3	64
4Q10	7		71
1Q11	3		74
2Q11	2	1	77
3Q11	2		79
4Q11	5		84
1Q12	10		94
2Q12	5		99
3Q12	3		102
4Q12	6		108
1Q13	5		113
2Q13	7		120
3Q13	11	2	133
4Q13	1	1	135
1Q14	4		139
2Q14	1		140

Table D. *University of Michigan* disproportionately affected populations (DAP) accruals by individual trials and accrual totals (as of 04/01/2014)

DOD#	White	African-American	White Hispanic	Total
c07-012	**13**	**3**		**16**
c08-001	**6**	**1**		**23**
c08-009	**12**			**35**
c09-024	**1**			**36**
c09-031	**5**	**1**		**42**
c09-033	**5**			**47**
c09-044	**6**			**53**
c09-057	**4**			**57**
c10-071	**8**			**65**
c10-072	**1**			**66**
c10-073	**3**			**69**
c11-079	**26**	**2**	**1**	**98**
c11-089	**24**	**3**		**125**
c12-104	**4**	**1**		**130**
c12-111	**8**			**138**
c14-135	**2**			**140**
Total	**128**	**11**	**1**	**140**
	91%	**8%**	**1%**	**100%**

Table E. The *University of Michigan* patient contribution to other DOD-PCCTC member trials (as of 04/01/2014)

UMich site led studies (Accrual #)		UMich site accruals to other consortium site led studies (Accrual #)	
c11-079 XL184	(29)	c10-073 Ced/Dasatinib	(3)
c09-044 TAK700	(6)	c09-033 Itraconazole	(5)
c09-057 EMD525797	(4)	c-08-009 Nab-docetaxel	(12)
c09-031 ABT-888	(6)	c10-071 Tesetaxel	(8)
c11-089 Gene fusion	(27)	c10-072 ARN-509	(1)
c08-001 IMC-A12	(7)	c07-012 AT-101	(16)
c12-111 PSMA	(8)	c12-104 BIND-014	(5)
c14-135 GDC-0068	(2)	c09-024 Pazopanib	(1)
Total	89		51
% total of accruals	**64**		**36%**

Table F. Personnel Receiving Pay From the Research Effort at the *University of Michigan* as of 04/01/2014)

Role	**Name**
Principal Investigator	Maha Hussain, MD
Co-Investigator	David C. Smith, MD
Co-Investigator	Kenneth J. Pienta, MD
Co-Investigator	Kathleen Cooney, MD
Co-Investigator	Ajjai Alva, MD (effective February 1, 2012)
Clinical Research Coordinator - Reg	Charles Leister
Clinical Research Administrator	Gregory Campbell
Research Nurse	Tamara Huebner
GU Data Manager	Patricia Jo Harvey
GU Data Manager	Amie Anderson (until June 1, 2012)
Biostatistician	Stephanie Daignault-Newton
IT Supervisor	Mathew Innes
Radiologist	Mahmoud Al-Hawary, MD (until January 31, 2013)
Radiologist	Matthew Davenport, MD (effective February 1, 2013)
Pathologist	Lakshmi Priya Kunju, MD (effective July 1,2013)
Radiologist	Morand Piert, MD (effective May 1, 2013)
Pathologist	Rohit Mehra, MD (effective August 1, 2013)
Financial Specialist	Susan Hansen (effective April 1, 2011)

Appendix A

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EMD 121974 in patients with nonmetastatic castration-resistant prostate cancer (CRPC) NCI-6735: A study by the DOD/PCF Prostate Cancer Clinical Trials Consortium.

Sub-category:
Prostate Cancer: Early/Localized disease, Locally Advanced/Recurrent/Advanced disease, and Biology
Category:
Prostate Cancer: Early/Localized disease, Locally Advanced/Recurrent/Advanced disease, and Biology
Meeting:
2010 Genitourinary Cancers Symposium
Session Type and Session Title:
Reception and General Poster Session B: Prostate Cancer
Abstract No:
152

Author(s):
A. S. Alva, S. F. Slovin, S. Daignault, M. A. Carducci, R. S. DiPaola, D. B. Agus, A. P. Chen, M. Hussain, DOD/PCF Prostate Cancer Clinical Trials Consortium; University of Michigan, Ann Arbor, MI; Memorial Sloan-Kettering Cancer Center, New York, NY; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD; The Cancer Institute of New Jersey, New Brunswick, NJ; University of Southern California, Beverly Hills, CA; National Cancer Institute, Bethesda, MD

Abstract:

Background: Integrins are cell surface molecules on endothelial and prostate cancer cells involved in migration and angiogenesis. EMD121974 (Cilengitide) is a selective antagonist of αvβ3, αvβ5 integrins. We conducted a phase II study of single agent EMD121974 in non-metastatic CRPC patients (pts) with rising PSA. **Methods:** Pts with nonmetastatic CRPC, PSA progression, minimum PSA ≥ 2 ng/mL, adequate organ function were observed for 4 wks after registration with PSA q2 wks then treated with 2,000 mg IV of EMD121974 twice weekly in q4 wk cycles. Blood for PSA, circulating tumor cells (CTC) and circulating endothelial cells (CEC) was collected each cycle. In the absence of toxicity/progression, pts were treated for a minimum of 3 cycles before response assessment. Primary end point was rate of confirmed PSA decrease by ≥ 50%. The study was designed to detect a RR of ≥ 20% with n = 32 pts. Secondary endpoints: safety, PSA slope, response duration, time to progression (TTP), overall survival (OS), changes in CTCs, CECs and integrin gene expression. Slow accrual stopped the study. **Results:** Of 16 pts registered, 1 progressed clinically pretreatment; 2 ineligible pts received treatment and were evaluated for toxicity. Median age was 65 years, median baseline PSA 8.4 ng/ml (2.2-77) and Gleason sum 7 (6-9). There were no PSA responses; 11 pts progressed (2 by imaging) after 3 cycles. Median PSA TTP was 1.8 months (95% CI:0.9,2.8), median OS 37 months. There was no effect on the PSA slope (median pretreatment PSA slope 1.1/month and post treatment median is 1.8/month). Treatment was well tolerated with 2 grade 3 toxicities (atrial fibrillation), no grade 4 toxicities and 27 grade 1/2 toxicities. Nine eligible pts had CTC data; CTCs were detected in 1/9. In 5 pts with baseline and progression CTC data, CTC increased from 0 to 1 (2 pts), stayed at 0 (2 pt) and decreased from 23 to 0 (1 pt). 10 eligible patients had CEC data at baseline with a median of 26 (range 0,61). At progression (n = 7), median CEC was 47 (range 15,148). **Conclusions:** EMD 121974 was well tolerated but had no clinical antitumor activity. CTCs were rare even with progression thus of questionable utility in this setting.

Appendix B

PC080189-2043

A PHASE 2 RANDOMIZED STUDY OF CIXUTUMUMAB (IMC-A12) OR RAMUCIRUMAB (IMC-1121B) PLUS MITOXANTRONE AND PREDNISONE IN PATIENTS (PTS) WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (CRPC) FOLLOWING DISEASE PROGRESSION ON DOCETAXEL-BASED CHEMOTHERAPY

Maha Hussain,1 Dana Rathkopf,2 Glenn Liu,3 Andrew J. Armstrong,4 William Kevin Kelly,5 Anna Ferrari,6 John Hainsworth,7 Ling Yang,8 Jonathan Schwartz,8 Hagop Youssoufian,8 and Celestia S. Higano9

1University of Michigan, Ann Arbor, 2Memorial Sloan-Kettering Cancer Center, 3University of Wisconsin Carbone Cancer Center, 4Duke University Medical Center, 5Yale University, 6New York University Cancer Institute, 7Sarah Cannon Cancer Center, 8ImClone Systems, Inc., and 9Fred Hutchinson Cancer Research Center

Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis and insulin-like growth factor (IGF-1R)-mediated signaling contribute to prostate cancer progression. Cixutumumab (CIX; IMCA12) is a fully human IgG1 recombinant monoclonal antibody (MAb) that specifically targets the human IGF-IR and ramucirumab (RAM; IMC-1121B) is a fully human IgG1 MAb that inhibits VEGF receptor-2 (VEGFR-2) binding and signaling. We investigated the safety and efficacy of CIX or RAM in combination with mitoxantrone (M) plus prednisone (P) in castration-resistant prostate cancer (CRPC) patients (pts) that had progressive disease (PD) on docetaxel.

Methods: Eligible pts had metastatic CRPC with PD during/within 120 days of docetaxel (defined as PD by RECIST, at least two new bone lesions, and/or increasing prostate specific antigen [PSA]), ECOG PS 0-2, PSA ≥ 2 ng/mL, and adequate organ function. All pts received M 12 mg/m2 IV on day 1 every 3 weeks + P 5 mg PO BID and were randomized to either CIX 6 mg/kg or RAM 6 mg/kg each administered intravenously weekly for up to 12 cycles. Tumor assessments were after the first three cycles, then every 6 weeks. The primary endpoint was composite progression-free survival (cPFS, as defined by RECIST, bone scan progression, new skeletal events, and other components, including death). Other endpoints were safety, response, overall survival (OS), and pharmacokinetic/pharmacodynamic profiles. Sample size was based on a targeted 50% improvement in median cPFS from 11.1 to 16.7 weeks, based on results presented from a large trial in chemotherapy refractory CRPC in which a similar cPFS was employed (SPARC; Sternberg et al. ASCO, 2007).

Results: Of 139 pts randomized, 132 received study treatment. The median age for the 66 pts on CIX was 65 years and for the 66 pts on RAM 68 years. The median PSA for CIX was 118.5 ng/mL and 113.8 ng/mL for RAM. Median number of cycles was 5 for CIX and 6 for RAM. Median duration of follow-up was 6.8 months (m) for CIX and 9.1 m for RAM. Nineteen pts continue to receive RX as of 7-29-10. The most frequently observed adverse events considered at least possibly related to study drug: for CIX included fatigue 59% (15% Grade [G] ≥3), nausea 38% (2% G≥3), and anorexia 33% (0 G≥3); for RAM included fatigue 58% (5% G≥3), nausea 35% (0 G≥3), and diarrhea 30% (2% G≥3). Preliminary median cPFS is 4.1m (2.2-6.3 m 95% CI [confidence interval]) on CIX and 7.4 m (4.5-9.3 m 95% CI) on RAM. Preliminary OS is 10.2 m (6.4-15.4 m 95% CI) on CIX and 13.0 m (9.3-16.7 m 95% CI) on RAM. Preliminary PSA response is the same for both arms at 21% (11%-34% 95% CI). Preliminary radiographic response rate (CR+PR) is 9.1% (3.4%-18.7% 95% CI) on CIX and 10.6% (4.4%-20.6% 95% CI) on RAM.

Conclusions: Both CIX/M/P and RAM/M/P were reasonably tolerated in CRPC. Preliminary PFS and OS of RAM/M/P appear encouraging, favoring further investigation of this regimen.

Impact: Therapeutic options in chemotherapy refractory prostate cancer are limited. The protocol investigated two novel regimens involving targeted monoclonal antibodies in combination with an established cytotoxic chemotherapy in pts with docetaxel-refractory CRPC. The addition of an anti-VEGFR2 antibody therapy to M/P appears encouraging and may be associated with enhanced efficacy and a favorable safety profile.

This work was supported by the U.S. Army Medical Research and Materiel Command under W81XWH-09-1-0146.

Appendix C

PC081610-1865

THE PROSTATE CANCER CLINICAL TRIALS CONSORTIUM: A COLLABORATIVE MULTICENTER PROSTATE CANCER RESEARCH MODEL

Howard I. Scher,[1] Tomasz M. Beer,[2] Michael A. Carducci,[3] Paul Corn,[4] Robert Dipaola,[5] Daniel J. George,[6] Andrea L. Harzstark,[7] Elisabeth I. Heath,[8] Celestia S. Higano,[9] Maha Hussain,[10] Michael J. Morris,[1] Susan F. Slovin,[1] Walter Stadler,[11] Mary-Ellen Taplin,[12] and George Wilding[13]

[1]Memorial Sloan-Kettering Cancer Center, [2]Oregon Health & Science University, [3]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, [4]University of Texas M. D. Anderson Cancer Center, [5]Cancer Institute of New Jersey, [6]Duke Comprehensive Cancer Center, [7]University of California, San Francisco Comprehensive Cancer Center, [8]Karmanos Cancer Institute, [9]University of Washington, [10]University of Michigan Cancer Center, [11]University of Chicago, [12]Dana-Farber Cancer Institute, and [13]University of Wisconsin Comprehensive Cancer Center

Background and Objectives: The Prostate Cancer Clinical Trials Consortium (PCCTC) was formed in 2006 by congressional mandate with support from the Department of Defense (DOD) Clinical Consortium Award and the Prostate Cancer Foundation (PCF) with the objective of streamlining early phase drug development, enhancing collaboration among prostate cancer research centers, and promoting clinical trial availability for patients. A novel infrastructure centered at Memorial Sloan-Kettering Cancer Center supports this consortium to design, review, prioritize, and conduct Phase I and Phase II trials. Additionally, PCCTC is spearheading an effort to develop novel biomarkers and explore new endpoints associated with its trials.

Methodologies: The initial PCF and DOD award funded the consortium for 3 years and was renewed in 2007 for 5 additional years. The consortium facilitates trial development between member sites, individual investigators, and research sponsors. To do so, a comprehensive suite of services and administrative, legal, and financial elements have been developed to manage and eliminate barriers to the design, activation, and completion of early-phase multicenter trials. Critical portfolio analysis centered on strategic growth has been initiated to drive the scientific agenda.

Results to Date: The PCCTC has expanded its membership from 8 to 13 National Cancer Institute-designated Comprehensive Cancer Centers. Unified protocol and consent language, standard endpoints (PCWG2), novel biomarkers, and the use of "Go-No Go" metrics have been developed and adopted. As of July 2010, more than 2,227 men with prostate cancer have been enrolled in consortium trials since inception. In this time, the PCCTC has reviewed 129 proposals, accepting 103 for activation, 45 of which have been completed. Principles for the analytical validation of biomarkers have been established within the PCCTC, and efforts to qualify circulating tumor cell (CTC) and imaging biomarkers have been embedded in consortium trials. The PCCTC has studied 10 agents in a succession of trials and crucially, advanced 5 therapeutic candidates to Phase III study.

Conclusion: The PCCTC fulfills a congressional directive to create an instrument dedicated to rapid accrual to early-phase, multicenter trials in prostate cancer. Centralized management of research activities has yielded an increased number of proposed trials and patients accrued, critical reviews of biomarkers, and notably, development in the Phase III space. With continued support from the DOD and PCF, the PCCTC is evaluating clinical and translational business models for sustainability into the future**Impact Statement:** The PCCTC is the first prostate cancer clinical consortium and has redefined the collaborative multicenter effort to develop novel therapies, endpoint, and biomarkers in prostate cancer.

This work was supported by the U.S. Army Medical Research and Materiel Command under W81XWH-09-1-0147 and the Prostate Cancer Foundation.

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Phase II study of AT-101 to abrogate Bcl-2-mediated resistance to androgen-deprivation therapy (ADT) in patients (pts) with newly diagnosed androgen-dependent metastatic prostate cancer (ADMPC).

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2011 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session B: Prostate Cancer
Abstract No:
137
Citation:
J Clin Oncol 29: 2011 (suppl 7; abstr 137)
Author(s):
M. N. Stein, I. Khan, M. Hussain, G. Liu, G. Wilding, E. M. Posadas, W. M. Stadler, C. Jeyamohan, S. Eddy, R. S. DiPaola, Prostate Cancer Clinical Trials Consortium; The Cancer Institute of New Jersey/University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; University of Michigan, Ann Arbor, MI; University of Wisconsin Carbone Cancer Center, Madison, WI; The University of Chicago Medical Center, Chicago, IL; The Cancer Institute of New Jersey, New Brunswick, NJ

Abstract:

Background: Preclinical studies demonstrate that Bcl-2 is over-expressed in most pts with prostate cancer, causes drug resistance to ADT, and that modulation of Bcl-2 improves sensitivity of tumor cells. We are conducting a phase II study for men with ADMPC to test the hypothesis that AT-101, a small molecule Bcl-2 inhibitor, improves clinical results of pts initiating ADT for metastatic prostate cancer. Building on results from SWOG 9346 (Hussain JCO 2006) demonstrating that PSA nadir after 7 mo of ADT predicts survival, we are using a novel phase II trial design, in which the primary endpoint is the percentage of patients with PSA ≤ 0.2 ng/ml at 7 mo of ADT plus AT-101. **Methods:** Pts had ADMPC, PSA > 5.0 ng/ml within 12 wks prior to registration and no prior ADT for metastatic disease. ADT with LHRH agonist and bicalutamide started 6 wks prior to initiation of oral AT-101, 20 mg/day for 21 days of 28 day cycle. Pts received up to 8 cycles of ADT and AT-101. A total of 55 pts were enrolled (to obtain 48 evaluable pts) to in a two stage design with null hypothesis 48% versus alternative 68% with PSA ≤ 0.2 at 7 mo. With $\alpha = 0.1$ and $\beta = 0.9$, > 27 pts meeting this endpoint are required to recommend further study. **Results:** 55 pts were enrolled, median age 61.5 y; Gleason score (GS) 6 (5%),GS 7 (30%), GS 8 (24%), and GS 9 (41%). 3 pts had visceral mets and the remaining pts had bone or nodal metastasis. 42 pts have discontinued (9 toxicity, 9 progression, 1 withdrew) or completed (n = 23) 7 mo of treatment. In intention to treat analysis, 11 of 42 pts (26%) met the primary endpoint 10, of 42 (23%) pts had PSA > 0.2 and < 4.0 ng/ml after 7 mo. Grade 1/2 toxicities (%) included fatigue (36/9), nausea (20/9), vomiting (13/7), anorexia (15/2), AST/ALT (25/5), hypercalcemia (9/0), constipation (13/3), dry skin (9/0), anemia (18/0), sensory neuropathy (7/7), vomiting (12/7), hyperglycemia (7/4). Grade 3 toxicities were sensory neuropathy 2 pts, GI obstruction 1 pt, syncope 1 pt. **Conclusions:** Although final study results are pending the analysis of pts currently on therapy, 26% of pts achieved an undetectable PSA at 7 mo in a population with aggressive disease (66% GS ≥ 8).

Appendix E

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A randomized phase II study of pazopanib in castrate-sensitive prostate cancer: A University of Chicago phase II consortium/DoD Prostate Cancer Clinical Trials Consortium study.

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2011 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session B: Prostate Cancer
Abstract No:
170
Citation:
J Clin Oncol 29: 2011 (suppl 7; abstr 170)
Author(s):
J. E. Ward, S. Limvorasak, T. Karrison, G. S. Chatta, M. Hussain, D. H. Shevrin, R. Z. Szmulewitz, W. M. Stadler, E. M. Posadas; The University of Chicago Medical Center, Chicago, IL; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Michigan, Ann Arbor, MI; NorthShore University Health System, Evanston, IL

Abstract:

Background: Intermittent androgen suppression (IAS) has been studied as a way of minimizing toxicity from long term androgen deprivation therapy (ADT). Based on previous studies with similar agents, we hypothesized that inhibition of VEGFR would result in prolonged time to PSA progression (TTPP) and allow for longer periods off ADT. **Methods:** Men with biochemically recurrent, progressive prostate cancer and no evidence of macroscopic metastases were enrolled. They received 6 months of ADT. If at the end of that time the PSA was <0.5 ng/mL (with castrate testosterone levels), they were randomized to pazopanib 800 mg/d or observation. The primary outcome was TTPP, defined as time to a PSA >4.0 ng/mL, at which time they were restarted on ADT. **Results:** 37 pts met randomization criteria. 18 were randomized to pazopanib. Only 4 pts met the endpoint criteria of TTPP, whereas 13 (72%) pts went off study for other reasons with 1 pt on treatment at study closure. Reasons for discontinuation included drug toxicity (grade 1/2, 9 pts) and patient preference (2 pts). No grade 3/4 toxicity was noted. 1 pt was removed due to pulmonary embolus, 1 pt due to MD discretion and 1 pt due to noncompliance. 19 pts were randomized to observation of which 12 were off treatment when the study was stopped. Only 5 pts met criteria for TTPP, whereas 7 of 12 (58%) dropped out for other reasons, including the frequency of protocol related blood draws and visits (3 pts) and randomization to observation (2 pts), 1 pt was removed per MD discretion and 1 pt transferred care. Due to high dropout rates in both arms, accrual was halted as the primary endpoint could not be measured robustly. **Conclusions:** Minimizing the long term toxicities of ADT is an unmet need in prostate cancer therapy. Hence clinical interventions in concert with IAS represent an attractive area for drug development. This trial has outlined several barriers that exist in studying this patient population and might help to optimize future studies. Future trial design in this arena should investigate drugs with minimal toxicity and employ a design that maximizes patient convenience while anticipating the low threshold for patient drop out.

Appendix F

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Phase II study of XL184 in a cohort of patients (pts) with castration-resistant prostate cancer (CRPC) and measurable soft tissue disease.

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2011 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session B: Prostate Cancer
Abstract No:
127
Citation:
J Clin Oncol 29: 2011 (suppl 7; abstr 127)
Author(s):
D. C. Smith, M. R. Smith, E. J. Small, C. Sweeney, R. Kurzrock, M. S. Gordon, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, M. Hussain; University of Michigan Cancer Center, Ann Arbor, MI; Massachusetts General Hospital Cancer Center, Boston, MA; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Pinnacle Oncology of Arizona, Scottsdale, AZ; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Exelixis, South San Francisco, CA; University of Michigan, Ann Arbor, MI

Abstract:

Background: XL184 is an oral, potent inhibitor of MET and VEGFR2. MET pathway activation promotes tumor growth, invasion and metastasis. Overexpression of MET and/or its ligand HGF are associated with prostate cancer metastasis. In preclinical studies, androgen ablation upregulates MET signaling. Preliminary data from the open label Lead-in Stage of an ongoing adaptive design phase II randomized discontinuation trial are presented. **Methods:** Eligible pts had CRPC, measurable disease with or without bone metastasis, and disease progression on ≤1 prior non-hormonal systemic treatment. XL184 was administered orally for 12 weeks (wks). Tumor (RECIST) and bone scan response (complete or partial resolution) were assessed every 6 wks. Primary endpoint is objective response rate at wk 12. Pts with SD at wk 12 will enter a placebo-controlled randomized phase. **Results:** As of 10/4/10, 72 pts have been enrolled. Median time on study was 50 days (range, 6+-350+ days). Median age was 69 yrs; 45% of pts were docetaxel-pretreated. All pts had measurable disease, including 69% with visceral metastases. To date, there are 24 response evaluable pts, defined as enrolled ≥12 wks prior to data cutoff. 5/24 (21%) pts had a partial response (≥30% reduction) in measurable disease with 3 responses confirmed at 12 wks and 2 unconfirmed responses ongoing. 6/24 (25%) had PSA declines of ≥50%. 13 of 15 (87%) pts with known bone metastases had either complete or partial resolution of lesions on bone scan. Bone scan responses were associated with investigator-reported improvement in bone pain in 11/15 (73%) with pain at baseline. Effects on osteoclast and osteoblast activity were observed: plasma C-telopeptide declined ≥50% in 8/12 (66%) pts and serum total alkaline phosphatase (tALP) declined ≥50% in 5/8 (63%) pts with bone metastases and baseline elevated tALP. The most common AEs ≥Grade 3 severity (related) were fatigue (10%), diarrhea (3%) and elevated AST (3%). **Conclusions:** XL184 results in tumor responses, partial or complete resolution of lesions on bone scan, and symptom relief in pts with metastatic CRPC, including those pretreated with docetaxel. XL184 also decreased biomarkers of both osteoblast and osteoclast activity.

406 Phase 2 study of XL184 in a cohort of patients (pts) with castration resistant prostate cancer (CRPC) and measurable soft tissue disease

POSTER

D.C. Smith A. Spira, J. De Grève, L. Hart, S. Holbrechts, C.C. Lin, M. Hussain, S. Herrick, K. Houggy, N. Vogelzang University of Michigan, Department of Medicine Ann Arbor USA; Fairfax Northern Virginia Hematology-Oncology PC, NA Fairfax USA; Universitair Ziekenhuis Brussel, Department of Medical Oncology Brussels

Background: XL184 is an oral potent inhibitor of MET, VEGFR2 and RET. Activation of the MET pathway promotes tumor growth, invasion, and metastasis. Overexpression of MET and/or its ligand HGF have been shown to correlate with prostate cancer metastasis to lymph nodes and bones, and disease recurrence. In addition, androgen ablation has been shown to upregulate MET signaling in preclinical studies. Targeting the MET pathway with XL184 may therefore be a promising treatment strategy. Preliminary data from the open label Lead-in Stage of a Phase 2 randomized discontinuation trial are presented showing the effects of XL184 in pts with CRPC.

Methods: Eligible pts have CRPC with measurable disease and have progressed on up to 1 prior non-hormonal systemic treatment after antiandrogen withdrawal. XL184 is administered open label at 100 mg free base equivalent (125 mg XL184-malate-salt) qd for 12 weeks (wks) (Lead-in Stage). Tumor response is assessed radiologically every 6 wks. Pts with partial or complete response (PR or CR) at wk 12 continue to receive XL184; pts with progressive disease (PD) discontinue XL184. Pts with SD at wk 12 are randomized 1:1 to receive XL184 or placebo. Cross-over from placebo to XL184 is allowed upon PD. Primary endpoints are objective response rate at wk 12 and progression free survival in the Randomized Stage. PSA levels will be correlated with clinical outcomes.

Results: A total of 16 pts have been enrolled with a median age of 69 years. The median number of prior non-hormonal systemic treatments was 1, with 7 pts receiving docetaxel. Of 9 pts who were evaluable (minimum 12 wks follow up) to date, 1 pt achieved a PR and 5 pts achieved SD for an overall disease control rate of 67% at wk 12. Two pts achieved a near complete resolution of tracer uptake on bone scan with one pt previously treated with docetaxel who attained a 41% reduction in measurable disease and a reduction of PSA > 50% at wk 12. Most frequently observed adverse events regardless of causality with CTCAE Grade ⩾3 in the Lead-in Stage were fatigue and asthenia (each n = 2).

Conclusions: Preliminary results suggest that XL184 is active in CRPC pts who failed prior treatment. XL184 was generally well tolerated. Updated efficacy and safety results will be presented.

Poster Presentation at the 22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Berlin, Germany 16-19 November, 2010.

Appendix H

2011 ASCO Annual Meeting

Maha Hussain

Logout

HOME

MY PRESENTATION

Oral Abstract Session: Genitourinary Cancer (Prostate)
Role: Presenter

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My Abstract

For your convenience, a copy of your submitted abstract is below.

Abstract ID (Temp. Abst. ID): 4516(82339)
Title: Cabozantinib (XL184) in metastatic castration resistant prostate cancer (mCRPC): Results from a phase 2 randomized discontinuation trial.
Author(s): M. Hussain, M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara Jr., C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, D. C. Smith
Abstract:
Background: Cabozantinib (Cabo) is an inhibitor of MET & VEGFR2. MET signaling promotes tumor growth, invasion & metastasis. **Methods:** mCRPC patients (pts) with progressive measurable disease (mRECIST) received Cabo at 100 mg qd PO over a 12 week (wk) Lead-in stage. Response was assessed q6 wks. Treatment ≥ wk 12 was based on response: pts with PR continued open-label Cabo, pts with SD were randomized to Cabo vs placebo, & pts with PD discontinued. Primary endpoint was objective response rate (ORR) per mRECIST in the Lead-in stage. Up to 200 pts could be enrolled to target 70 randomizations. Bone scans (b-scans) were independently reviewed. **Results:** Accrual was halted at 168 pts based on an observed high rate of clinical activity. 100 pts are currently evaluable for the Lead-in stage; median age 68, 47% with visceral disease, 78% with bone metastasis, & 47% docetaxel (D) pretreated. Median f/u was 4 months (range, 1-15); median PFS not yet reached. Most common related Grade 3/4 AEs were fatigue (11%), HTN (7%), & hand-foot syndrome (5%); no related Grade 5 AEs reported. Dose reductions for AEs occurred in 51% of pts, & discontinuations in 10%. **Bone effects:** 86% (56/65 pts evaluable by b-scan) had complete or partial resolution of lesions on b-scan as early as wk 6. Eight pts (12%) had SD & 1 pt (2%) had PD. In 28 pts receiving narcotics for bone pain, 64% had improved pain & 46% decreased or halted narcotics, per investigator. Median maximum rise in hemoglobin in anemic pts (Hb < 11 g/dL) was 2.2 g/dL (range, 0.6-3.5). Osteoclast & osteoblast effects were observed: 55% had declines of ≥50% in plasma C-Telopeptide; 56% of pts with elevated tALP had declines of ≥50%. **Soft tissue effects:** Objective tumor shrinkage occurred in 84% of pts. ORR at wk 12 was 5%, 3 additional PRs await confirmation. PSA changes were independent of clinical activity. Overall, wk 12 disease control rate (PR+SD) was 71%. Randomization was halted & pts unblinded due to high rates of b-scan resolution & pain relief. **Conclusions:** Cabo showed clinical activity regardless of prior D in mCPRC pts, particularly in pts with bone disease, as reflected by high rates of b-scan resolution & pain relief, in addition to improvements in Hb & tumor regression.

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Appendix I

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A phase II randomized study of cixutumumab (IMC-A12: CIX) or ramucirumab (IMC-1121B: RAM) plus mitoxantrone (M) and prednisone (P) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following disease progression (PD) on docetaxel (DCT) therapy.

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Session Type and Session Title:
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Abstract No:
97
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Author(s):
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Abstract Disclosures

Abstract:

Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis and insulin-like growth factor (IGF-IR)-mediated signaling contribute to mCRPC growth. CIX and RAM are fully human IgG1 human monoclonal antibodies targeting IGF-IR and VEGF receptor-2 (VEGFR-2) respectively. We investigated the safety and efficacy of CIX or RAM in combination with M + P in mCRPC pts with PD on DCT. **Methods:** Eligible pts had mCRPC and PD during/within 120 days of DCT, ECOG PS 0-2, PSA ≥ 2 ng/mL, and adequate organ function. All pts received M 12 mg/m^2 IV every 3 weeks (w) + P 5 mg PO BID for up to 12 cycles and were randomized to either CIX 6 mg/kg or RAM 6 mg/kg IV q w. Tumor assessments were after the first 3 cycles and then q6w. Primary endpoint was composite progression-free survival (cPFS: either RECIST PD, bone scan PD or new skeletal events). Other endpoints included safety, response and overall survival (OS). Sample size was based on a targeted 50% increase in median (mdn) cPFS from 2.6 months (m) to 3.9 m. **Results:** 132 pts were treated; 66 each to CIX or RAM. Mdn age and baseline PSA was 65 yr and 129 ng/mL for pts treated with CIX and 68 yr and 111 ng/mL for RAM. Involvement of sites other than bone was CIX: 79% and RAM: 70%. The most frequent Grade ≥3 related adverse events for CIX/M/P: fatigue 17%, leukopenia 12%, and neutropenia 8%, and for RAM/M/P: leukopenia 8%, neutropenia 8% and hypertension 8%. Left ventricular dysfunction/CHF: 12% for CIX (0% G3) and 23% for RAM (8% G3). Mdn number of Rx cycles were 5 for CIX and 6 for RAM. Mdn follow-up was 22.7 m for CIX and 21.8 m for RAM. PSA response was 18.4% (8.8-32% 95% CI) on CIX and 22.0% (11.5-36% 95% CI) on RAM. Mdn cPFS and OS were 4.1 m (3.0-5.6 m 95% CI) and 10.8 m (6.5-13.0 m 95% CI) for CIX and 6.7 m (4.5-8.3 m 95% CI) and 13.0 m (9.5-16.0 m 95% CI) for RAM. **Conclusions:** CIX/M/P and RAM/M/P were reasonably tolerated and achieved the primary endpoint. Preliminary cPFS and OS of RAM/M/P appear encouraging; sustained disease control was observed in pts on both rx arms. Correlation of serum markers of IGF and VEGF activity with clinical endpoints is planned.

Appendix J

American Society of Clinical Oncology
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Pilot study of veliparib (ABT-888) with temozolomide (TMZ) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
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2012 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session C: Prostate Cancer
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J Clin Oncol 30, 2012 (suppl 5; abstr 224)
Author(s):
Maha Hussain, Michael Anthony Carducci, Susan F. Slovin, Jeremy Paul Cetnar, Jiang Qian, Evelyn Mary McKeegan, Elizabeth Litvinovich, Brenda Chyla, Robert Hetman, Bhardwaj Desai, Vincent L. Giranda, Joshi J. Alumkal; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; University of Wisconsin, Madison, WI; Abbott Laboratories, Abbott Park, IL; Oregon Health and Science University, Portland, OR

Abstract Disclosures

Abstract:

Background: Castration-resistant PC tumors exhibit increased PARP activity (critical enzymes for DNA damage repair). Veliparib is a novel, oral, potent inhibitor of PARP-1 and PARP-2. Preclinically, resistance to oral TMZ treatment in the PC3-Luc prostate cancer mouse model was reversed when mice were treated with veliparib. Based on the synergistic interaction, we evaluated the efficacy and safety of veliparib + TMZ in mCRPC pts. **Methods:** Eligible pts had mCRPC, PSA>2 ng/mL, progressed on at least one docetaxel based therapy and adequate organ function. Pts received veliparib 40 mg BID Days (D) 1-7 and TMZ D1-5 in 28D cycle (C) until disease progression (PD) or unacceptable toxicities. Tumor response was assessed every 8 weeks. Primary objective: Efficacy based on rate of PSA decline of 30% or greater. Secondary objectives: safety, RECIST objective response rate, progression-free survival (PFS), overall survival (OS) and biomarker analyses. A sample size of 25 pts provided 76% power to differentiate between PSA response rates of 5 and 20% at 1-sided type I error rate of 0.1. **Results:** 26 pts were enrolled; median age 67 years [55, 81]; median baseline PSA 107 ng/ml (6.9, 4584.4); 7/26 (27%) had 2 prior therapies. Median Cs of veliparib + TMZ received were 2 (range 1-9). Most frequent treatment related adverse events (AE) were fatigue (50%), nausea (38%) and constipation (23%). Grade 3/4 AEs in >10% of pts was thrombocytopenia (15%). All pts are off therapy. 25 pts were PSA response evaluable; 2 pts had a confirmed PSA response; 1 pt had a 37% decrease in PSA while the other pt had a 96% decrease in PSA and a 40% reduction in tumor size. 4/25 pts had stable disease for a minimum of 4 months (m). Median PFS was 2.1 m [95% CI: 1.8, 3.9]; 11/26 pts have died with median OS of 9.1 m [95% CI: 5.5, 11.7]. There was a negative correlation between change from baseline in circulating tumor cells and PFS. **Conclusions:** Veliparib + TMZ were well tolerated with evidence of some activity. Due to lack of activity of TMZ in CRPC,veliparib-induced potentiation of TMZ may not be clinically significant. Other combinations will be explored with higher doses of veliparib. Biomarker data will be presented.

Appendix K

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A noncomparative randomized phase II study of two dose levels of itraconazole in men with metastatic castration-resistant prostate cancer (mCRPC): A DOD/PCCTC trial.

Sub-category:
Prostate Cancer
Category:
Genitourinary Cancer
Meeting:
2011 ASCO Annual Meeting
Session Type and Session Title:
Poster Discussion Session, Genitourinary (Prostate) Cancer
Abstract No:
4532
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Author(s):
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Abstract Disclosures

Abstract:

Background: The antifungal drug itraconazole inhibits angiogenesis and Hedgehog signaling, and delays tumor growth in murine prostate cancer xenograft models. Unlike ketoconazole, it does not suppress adrenal androgen synthesis. **Methods:** A phase II study of oral itraconazole in men with chemo-naïve mCRPC (30% ketoconazole-pretreated) was conducted in 4 PCCTC sites. Men were randomized to low dose (LD) or high dose (HD) itraconazole (200 or 600 mg/d) until disease progression or unacceptable toxicity. The primary endpoint was PSA progression-free survival (PPFS) at 24 wk (PSA progression = 25% PSA rise above baseline/nadir; PCWG2 criteria); a 45% success rate in either arm was prespecified as constituting clinical significance. Secondary endpoints were progression-free survival (PFS) at 24 wk (progression = clinical/radiographic progression or death, but not rising PSA; PCWG2 criteria); median PFS; median PPFS; and max PSA decline. Exploratory outcomes were CTC enumeration, and analysis of serum testosterone (T) and DHEA-S. **Results:** The HD arm enrolled to completion (N=29), but the LD arm closed early (N=17) due to a prespecified futility analysis. After a median follow-up of 21.6 wk (HD arm) and 11.9 wk (LD arm), 24/29 and 17/17 men were evaluable for the primary endpoint. Efficacy results are shown below. In addition, 3/5 men (60%) in the HD arm and 2/3 men (67%) in the LD arm with unfavorable (≥5) CTCs at baseline converted to favorable (<5) CTC counts with treatment. Itraconazole did not reduce serum T or DHEA-S levels. Common toxicities (≥20%) were fatigue, nausea, anorexia, rash, and hypokalemia/hypertension/edema. **Conclusions:** Only the HD arm met its primary endpoint. Itraconazole 600 mg/d has single-agent activity in men with mCRPC that is not mediated by androgen suppression, and warrants further study.

Endpoint	Dose	Value	95% CI
Primary			
PPFS at 24 wk (%)	LD	11.8	3.2-43.2
	HD	48.4	32.1-73.0
Secondary			
PFS at 24 wk (%)	LD	18.8	6.8-52.0
	HD	61.1	44.1-84.6
Median PFS (wk)	LD	11.9	11.9-29.1
	HD	35.9	13.0-60+
Median PPFS (wk)	LD	11.9	5.6-20.0
	HD	17.0	12.4-29.0
≥30% PSA decline (%)	LD	5.9	0.2-28.7
	HD	28.6	13.2-48.7
≥50% PSA decline (%)	LD	0	0-19.5
	HD	14.3	4.0-32.7

Appendix L

American Society of Clinical Oncology
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Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial.

Sub-category:
Prostate Cancer
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Author(s):
M. Hussain, M. R. Smith, C. Sweeney, P. G. Corn, A. Elfiky, M. S. Gordon, N. B. Haas, A. L. Harzstark, R. Kurzrock, P. Lara, C. Lin, A. Sella, E. J. Small, A. I. Spira, U. N. Vaishampayan, N. J. Vogelzang, C. Scheffold, M. D. Ballinger, F. Schimmoller, D. C. Smith; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; University of Texas M. D. Anderson Cancer Center, Houston, TX; Pinnacle Oncology Hematology, Scottsdale, AZ; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of California, San Francisco, San Francisco, CA; University of California, Davis, Sacramento, CA; National Taiwan University Hospital, Taipei, Taiwan; Assaf Harofeh Medical Center, Zerifin, Israel; US Oncology Research, LLC, The Woodlands, TX; Virginia Cancer Specialists, PC, Fairfax, VA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Exelixis, South San Francisco, CA; University of Michigan Cancer Center, Ann Arbor, MI

Abstract Disclosures

Abstract:

Background: Cabozantinib (Cabo) is an inhibitor of MET and VEGFR2. MET signaling promotes tumor growth, invasion and metastasis. **Methods:** mCRPC patients (pts) with progressive measurable disease (mRECIST) received Cabo at 100 mg qd PO over a 12 week (wk) lead-in stage. Response was assessed q6 wks. Treatment ≥ wk 12 was based on response: pts with PR continued open-label Cabo, pts with SD were randomized to Cabo vs placebo, and pts with PD discontinued. Primary endpoint was objective response rate (ORR) per mRECIST in the lead-in stage. Up to 200 pts could be enrolled to target 70 randomizations. Bone scans (b-scans) were independently reviewed. **Results:** Accrual was halted at 168 pts based on an observed high rate of clinical activity. 100 pts are currently evaluable for the lead-in stage; median age 68, 47% with visceral disease, 78% with bone metastasis, and 47% docetaxel (D) pretreated. Median f/u was 4 months (range, 1-15); median PFS not yet reached. Most common related Grade 3/4 AEs were fatigue (11%), HTN (7%), and hand-foot syndrome (5%); no related Grade 5 AEs reported. Dose reductions for AEs occurred in 51% of pts, and discontinuations in 10%. Bone effects: 86% (56/65 pts evaluable by b-scan) had complete or partial resolution of lesions on b-scan as early as wk 6. Eight pts (12%) had SD and 1 pt (2%) had PD. In 28 pts receiving narcotics for bone pain, 64% had improved pain and 46% decreased or halted narcotics, per investigator. Median maximum rise in hemoglobin in anemic pts (Hb < 11 g/dL) was 2.2 g/dL (range, 0.6-3.5). Osteoclast and osteoblast effects were observed: 55% had declines of ≥50% in plasma C-Telopeptide; 56% of pts with elevated tALP had declines of ≥50%. Soft tissue effects: Objective tumor shrinkage occurred in 84% of pts. ORR at wk 12 was 5%; 3 additional PRs await confirmation. PSA changes were independent of clinical activity. Overall, wk 12 disease control rate (PR+SD) was 71%. Randomization was halted and pts unblinded due to high rates of b-scan resolution and pain relief. **Conclusions:** Cabo showed clinical activity regardless of prior D in mCPRC pts, particularly in pts with bone disease, as reflected by high rates of b-scan resolution and pain relief, in addition to improvements in Hb and tumor regression.

Poster 124

Activity and Safety of the Investigational Agent Orteronel in Men With Nonmetastatic Castration-resistant Prostate Cancer and Rising Prostate-specific Antigen: Results of a Phase 2 Study

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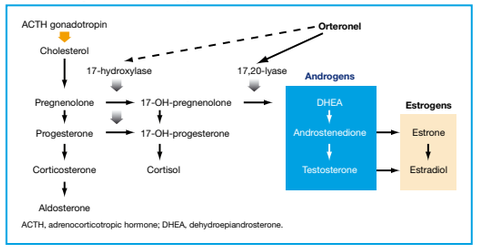
BACKGROUND

- Nonmetastatic, castration-resistant prostate cancer (nmCRPC) is an area of unmet medical need.[1–6]
- The only disease manifestation is rising prostate-specific antigen (PSA).[1]
- Median metastasis-free survival is ~30 months.[1]
  - One mechanism for castration resistance is the conversion of gonadal, adrenal, and tumoral androgen precursors to androgens, which results in tumor progression.[2–4]
- Orteronel (TAK-700) is an investigational, selective, non-steroidal inhibitor of 17,20-lyase, a key enzyme in the production of steroidal hormones (Figure 1).
  - In preclinical studies, orteronel inhibited 17,20-lyase activity more than 17-hydroxylase, with IC_{50} values of 140 nmol/L (95% CI: 120, 170) and 760 (640, 910), respectively, with minimal effect on CYP drug-metabolizing enzymes.[7]
- Orteronel has limited inhibition of 17α-hydroxylase, and may have less effect on cortisol synthesis, reducing the potential for mineralocorticoid excess, and has potential to allow for steroid-free dosing, making orteronel an attractive drug for longer durations of therapy.

Figure 1. Pathway of steroid hormone synthesis



ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone.

OBJECTIVES

Primary:

- The percentage of nmCRPC patients achieving a PSA reduction to ≤0.2 ng/mL (undetectable levels) after 3 months.

Secondary:

- Safety of orteronel
- PSA response rates at 3 and 6 months (decline in PSA of ≥90%, ≥50%, and/or ≥30%)
- The percentage who achieve a PSA ≤0.2 ng/mL after 6 months
- Time to PSA progression, time to metastases, and duration of progression-free survival (PFS)
- Changes in endocrine markers: serum testosterone, ACTH, DHEA, leuteinizing hormone (LH), corticosterone, and cortisol concentrations.

Exploratory:

- Exploratory endpoints include analysis of circulating tumor cells (CTC).
- Other candidate biomarkers (not yet available).

METHODS

Key eligibility

Entry criteria:

- Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma without radiographic evidence of metastasis
- nmCRPC with progression as reflected by baseline PSA ≥2 ng/mL and a doubling time ≤8 months, or PSA ≥8 ng/mL with a doubling time >8 months
- ≥18 years of age
- Surgical or ongoing medical castration, with testosterone <50 ng/dL.

Exclusion criteria:

- Prior therapy with aminoglutethimide or ketoconazole
- Antiandrogen therapy within 4 weeks (flutamide) and 6 weeks (all others)
- Prior chemotherapy for prostate cancer other than in the adjuvant setting
- Radiation therapy for prostate cancer within 30 days prior.

Study design and treatment

- Orteronel 300 mg BID treatment without prednisone was evaluated in men with nmCRPC and rising PSA.
- Patients received orteronel at 300 mg BID in 28-day treatment cycles.
- Orteronel therapy was continued until PSA progression, metastases, or unacceptable toxicities.

Assessments

- Physical exam and radiologic evaluations (CT/MRI) at screening assessed underlying disease status at study entry.
  - Evaluated at cycle 4, 7, 10, 13, and every 4th cycle until end of treatment.
- Toxicity according to NCI-CTCAE v4.03.
- Serum PSA levels at screening, at day 1 of cycles 1–7, 10, 13, and every 3rd cycle until PSA progression.
- Adrenal function was assessed on day 1 of cycles 1–7, 10, 13, and every 6 cycles thereafter, and included plasma ACTH, serum cortisol, DHEA, LH, corticosterone, and testosterone.

Endpoint definitions

- Primary endpoint: The percentage of nmCRPC patients achieving a PSA reduction to ≤0.2 ng/mL (undetectable levels) after 3 months.
- PSA progression: A 25% increase over the baseline/nadir concentration on two consecutive measurements at least 1 week apart and an absolute PSA increase ≥2 ng/mL.
- PFS: Time from first dose to first PSA progression, metastasis or death.
- PSA response rate: Percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), ≥30% (PSA30).
- Metastasis: ≥2 new lesions on bone imaging or 1 new lesion on soft tissue imaging.
- Time to metastasis: Time from first dose to first occurence of metastasis.

Statistical considerations

Sample size

- 38 patients provided 90% power to give a 1-sided significance level of 0.1 (H_0 5% vs. H_a 20%) for the percentage of patients achieving a PSA of ≤0.2 ng/mL after 3 months of orter onel treatment.

Population for analysis

- PSA response rate: patients with nmCRPC, PSA entry criteria, baseline and ≥1 post-baseline PSA measurement (N=38).
- Safety and time to event: patients with ≥1 dose of study drug (N=39).

Efficacy analysis

- Patients who achieve PSA of ≤0.2 ng/mL and had PSA assesments (PSA90, PSA50, PSA30).
- Time-to-event: Kaplan-Meier estimate of median, 6, and 12 month PFS.

RESULTS

- Data are presented as of December 15, 2011 and the study is currently ongoing.
- Patient demographics and disease characteristics are shown in Table 1.

Table 1. Baseline patient demographics

Characteristic	N=39
Median age, years (range)	71 (53–81)
Race (n, %)	
White	35 (90)
Black	4 (10)
ECOG performance status (n, %)	
0	33 (85)
1	6 (15)
Median (range)	
PSA	12.1 ng/mL (2.6–67.8)
Testosterone	7.9 ng/dL (1.4–17.3)
ACTH (n=33)	19.0 ng/L (0–47)

Safety

- Adverse events (AEs) were reported in 36 men (92%; Table 2).
- No grade 4 or 5 AEs were observed.
- 2 patients discontinued treatment for grade 2 adrenal insufficiency; upon review of the data, only 1 patient had laboratory values consistent with a hypoadrenal state.

Table 2. Most common treatment-emergent AEs reported in ≥20% of patients or grade 3 in ≥5% of patients

	Orteronel 300 mg BID (n=39)		
AE	All (n, %)	Grade 1/2	Grade 3
Fatigue	23 (59)	21 (54)	2 (5)
Diarrhea	15 (38)	14 (36)	1 (3)
Nausea	14 (36)	14 (36)	–
Hypertension	13 (33)	8 (21)	5 (13)
Decreased appetite	12 (31)	12 (31)	–
Constipation	11 (28)	11 (28)	–
Dyspnea	9 (23)	6 (15)	3 (8)
Cough	9 (23)	9 (23)	–
Vomiting	9 (23)	9 (23)	–
Dysgeusia	8 (21)	8 (21)	–
Dyspepsia	8 (21)	8 (21)	–
Hypokalemia	6 (15)	4 (10)	2 (5)
Pneumonitis	3 (8)	1 (3)	2 (5)

Serious AEs: 7 men (18%); 6 drug-related; most common pneumonitis (2 grade 3; 1 at grade 2); others included dyspnea, hypoxia, pulmonary embolism, atrial fibrillation, atrial flutter, adrenal insufficiency, and syncope (1 each). Discontinuations in 8 men due to AEs: dyspnea, pneumonitis, adrenal insufficiency, fatigue, hypertension (2 each), and diarrhea (n=1); 3 patients had dose reduction due to AEs: 1 patient due to left ventricular dysfunction, brain natriuretic peptide increased, sinus bradycardia, and atrioventricular block first degree; 1 patient due to diarrhea and vomiting; 1 patient due to fatigue and decreased appetite.

Treatment summary

- 17 men (44%) were on treatment for >6 months at the time of data cut-off.
- Median number of treatment cycles: 6 (range 1–17).

Efficacy summary

PSA response

- 6 men (16%) achieved PSA ≤0.2 ng/mL at 3 months.
- 32% of patients experienced a PSA90 at 3 months.
- 76% of patients experienced a PSA50 at 3 months.
- PSA response rate at 3 and 6 months of treatment are summarized in Table 3.
- Waterfall plot of maximum PSA change at any time on treatment is shown in Figure 2.
- Waterfall plots of PSA change at 3 and 6 months are shown in Figure 3.

Table 3. PSA response rate at 3 and 6 months

	3 months		6 months	
N=38	n (%)	(80% exact CI)	n (%)	(80% exact CI)
PSA ≤0.2ng/mL	6 (16)	(9, 26)	2 (5)	(1, 13)
PSA90	12 (32)	(22, 43)	8 (21)	(13, 32)
PSA50	29 (76)	(65, 85)	17 (45)	(34, 56)
PSA30	31 (82)	(71, 89)	20 (53)	(41, 64)

PSA response rate: percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), ≥30% (PSA30).

Figure 2. Waterfall plot of maximum PSA response at any time on treatment

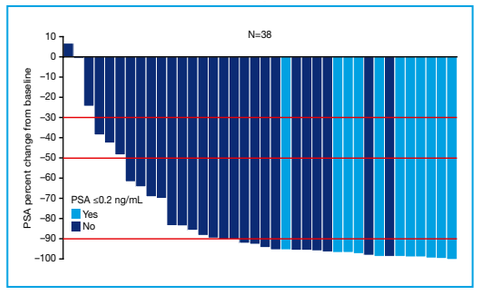
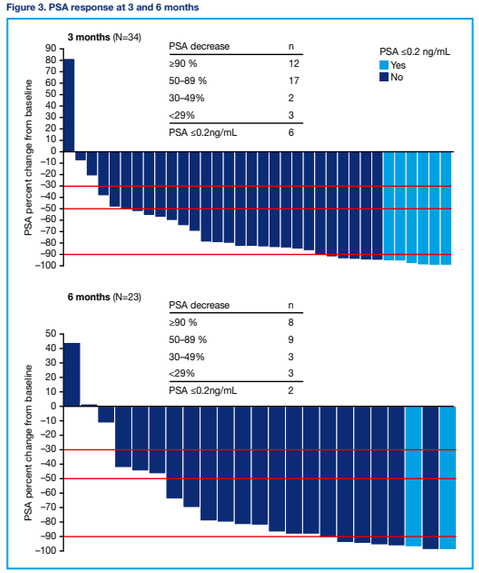


Figure 3. PSA response at 3 and 6 months



PSA progression

- Kaplan-Meier estimates of freedom from PSA progression were 97%, 91%, and 55% at 3, 6, and 12 months, respectively.
- Median time to PSA progression was 14.8 months (Figure 4).
- Duration of PSA response, as measured from time from first PSA response to protocol-defined PSA progression, is shown in Figure 5 for men who achieved PSA50 and PSA90 responses.

Figure 4. Kaplan-Meier time-to-PSA progression

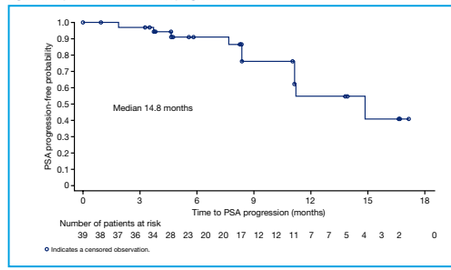
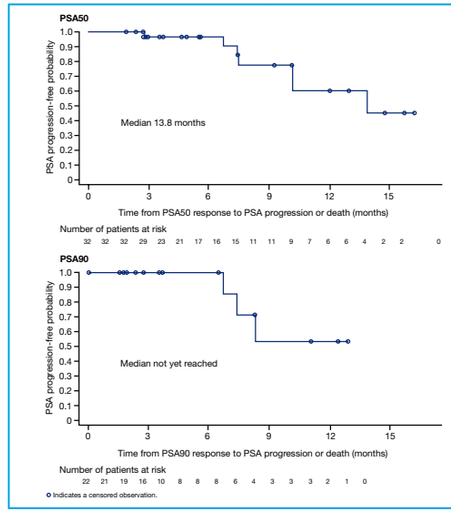


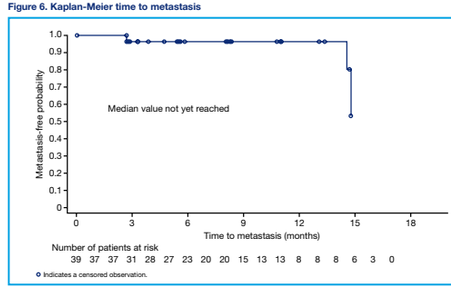
Figure 5. Kaplan–Meier duration of PSA50 and PSA90 response



Time to metastasis

- Kaplan-Meier estimates of freedom from metastasis is 97% for patients at 6 and 12 months (n=20, n=8, respectively, Figure 6).

Figure 6. Kaplan-Meier time to metastasis

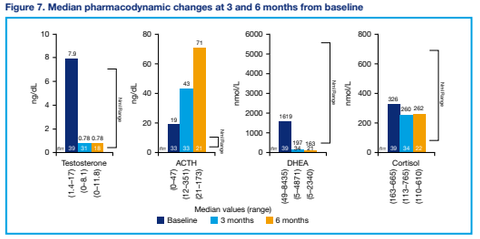


Endocrine markers

- Pharmacodynamic responses for serum testosterone, DHEA, ACTH, and cortisol are shown in Figure 7.
  - Testosterone decreased by 88–89%.*
  - ACTH increased by ~2–3-fold.
  - DHEA decreased by 85–90%.
  - Cortisol decreased by 21–32%.

*Percent change from baseline is based on the number of patients with both baseline and post-baseline values at that cycle.

Figure 7. Median pharmacodynamic changes at 3 and 6 months from baseline



Circulating tumor cells

- 7 patients had ≥1 CTC at baseline assessment (Table 4).
  - 1 patient had ≥5 cells/7.5 mL at baseline and converted to <5 cells/7.5 mL at the 3, 6, and 12 month assessments.
  - No patients had ≥5 cells after baseline during orteronel treatment.

Table 4. CTC assessments

	Time of assessment			
	Baseline	3 months	6 months	12 months
Patients assessed (n)	36	33	21	9
Number of CTCs	Patients with CTCs (n)			
1–4 CTCs	6	2	1	0
≥5 CTCs	1	0	0	0

CONCLUSIONS

- In patients with nmCRPC and rising PSA, single agent oral orteronel at a dose of 300 mg BID without prednisone was feasible and had manageable toxicities.
- After 3 months of orteronel treatment, 16% achieved PSA ≤0.2 ng/mL.
  - 76% achieved ≥50% decrease in PSA and 32% achieved a PSA reduction of ≥90%.
- Median time to PSA progression was 14.8 months.
- With a median follow up of 6 cycles (5.5 months), only 3 patients developed systemic metastasis and median time to metastasis was not reached.
- Fatigue, diarrhea, and nausea were the most common AEs.
  - All AEs were grade ≤3.
- Orteronel without prednisone suppressed adrenal androgens (testosterone and DHEA) by 85–90%.
  - Although ACTH was increased, median cortisol levels were decreased and remained within the normal range.
  - Although 2 patients discontinued treatment for "adrenal insufficiency", only 1 had laboratory values consistent with a hypoadrenal state for which he received corticosteroid replacement.

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Research was funded by Millennium Pharmaceuticals, Inc.

ClinicalTrial.gov identification number: NCT01046916.

Poster presented at the 27th Annual European Association of Urology, Paris, France, February 24–28, 2012.

APPENDIX M
Abstract #124

This abstract was presented during the past27th Annual Congress of the European Association of Urology	
Type:	**Poster Session**
Session:	**Treatment of advanced prostate cancer**
Date:	**Saturday February 25, 2012 from 14:15 to 15:45**
Room:	**Room Concorde Centre - Level 4**

Activity and safety of the investigational agent orteronel (ortl, TAK-700) in men with nonmetastatic castration-resistant prostate cancer (CRPC) and rising prostate-specific antigen (PSA): Results of a phase 2 study

Hussain, M.[1], Corn, P.[2], Michaelson, D.[3], Hammers, H.[4], Alumkal, J.[5], Ryan, C.[6], Bruce, J.[7], Moran, S.[8], Mortimer, P.[9], Lee, S.Y.[10], George, D.[11]

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Introduction & Objectives

Androgen signaling continues to be important in CRPC. Ortl is an investigational, oral, non-steroidal, selective 17,20-lyase inhibitor that suppresses androgen production and is in development for CRPC. Ortl has limited inhibition of 17α-hydroxylase, and may have less effect on cortisol synthesis, allowing steroid-free dosing. We evaluated ortl 300mg BID in men with nonmetastatic CRPC and rising PSA (NCT01046916).

Material & Methods

Eligible men had baseline PSA ≥2ng/mL + doubling time ≤8 mo or PSA ≥8ng/mL + doubling time >8 mo, and surgical or ongoing medical castration, with testosterone <50ng/dL. Prior chemotherapy, aminoglutethimide or ketoconazole, or concomitant corticosteroids were excluded. Starting dose was 300mg BID given continuously in 28-d cycles, optionally increasing to 400mg BID if ≥50% decrease in PSA (PSA50) was not achieved after 3 mo. Ortl was continued until PSA progression or metastases. The primary endpoint is the percentage of men with PSA ≤0.2ng/mL after 3 mo. 38 patients will provide 90% power for 1-sided significance level of 0.1 (H_0 5% vs. H_A 20%). Other endpoints include safety, 3 and 6 mo PSA30, PSA50, PSA90 rates, progression-free survival, time to PSA progression, time to metastases, changes in endocrine markers and circulating tumor cell (CTCs).

Results

38 men with a median age 71 y (range 55-81), ECOG PS 0/1 (84%/16%), median PSA 12.5ng/mL (2.6-67.8), testosterone 0.267nmol/L (0.05-0.60), and ACTH 19.5ng/L (n=32; 0-47) were treated. Median number of cycles was 5.5 (1-13); 1 patient had dose reduction due to adverse events (AEs), 1 had dose increase to 400mg BID. 99% of the total planned dose was taken. Gr ≥3 AEs occurred in 16 men (drug-related in 13); most common (≥5%) were dyspnea (11%), hypertension (8%), fatigue, hypokalemia, pneumonitis (5% ea). Seven men (18%) had serious AEs; most common was pneumonitis (2=Gr3, 1=Gr2). Eight men discontinued ortl due to AEs (dyspnea, pneumonitis, adrenal insufficiency, fatigue, hypertension, diarrhea, dysgeusia). At 3 mo, 4 men (11%) achieved PSA ≤0.2ng/mL. PSA50 and PSA90 rates were 69% and 28%, respectively. At 3 mo, median PSA decline was 83% to 1.96ng/mL (n=28; 0.12-50.5); median testosterone declined by 89% to 0.026nmol/L (0-0.28), and median ACTH increased by 228% to 55ng/L (12-351). Similar results were seen at 6 mo, with changes of –87% to 2.05ng/mL (0.1-12.3), –86% to 0.033nmol/L (0.01-0.41), and +312% to 83.5ng/L (21-173), respectively. 6-mo PSA50 and PSA90 rates were 42% and 17%, respectively. 14 men (37%) were on treatment >6 mo. Of 35 men with baseline CTC/7.5mL values, only 1 had CTC ≥5 and 6 had 1-4 CTC.

Conclusions

Ortl given without steroids is feasible in men with nonmetastatic CRPC, has manageable toxicities, and produces substantial and durable declines in testosterone and PSA.

Appendix N

Cabozantinib (XL184) in chemotherapy-pretreated metastatic castration resistant prostate cancer (mCRPC): Results from a phase II nonrandomized expansion cohort (NRE).

Subcategory:

Prostate Cancer

Category:

Genitourinary Cancer

Meeting:

2012 ASCO Annual Meeting

Session Type and Session Title:

Oral Abstract Session, Genitourinary Cancer (Prostate)

Abstract Number:

4513

Citation:

J Clin Oncol 30, 2012 (suppl; abstr 4513)

Author(s):

Matthew Raymond Smith, Christopher Sweeney, Dana E. Rathkopf, Howard I. Scher, Christopher Logothetis, Daniel J. George, Celestia S. Higano, Evan Y. Yu, Andrea Lynne Harzstark, Eric Jay Small, A. Oliver Sartor, Michael S. Gordon, Nicholas J. Vogelzang, David C. Smith, Maha Hussain, Johann Sebastian De Bono, Naomi B. Haas, Christian Scheffold, Yihua Lee, Paul G. Corn; Massachusetts General Hospital Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY; University of Texas M. D. Anderson Cancer Center, Houston, TX; Duke University Medical Center, Durham, NC; Fred Hutchinson Cancer Research Center, Seattle, WA; University of California, San Francisco, San Francisco, CA; Tulane Cancer Center, New Orleans, LA; Pinnacle Oncology Hematology, Scottsdale, AZ; US Oncology Research/Comprehensive Cancer Centers NV, Las Vegas, NV; University of Michigan, Ann Arbor, MI; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Royal Marsden Hospital and

Institute of Cancer Research, Sutton, United Kingdom; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; Exelixis, South San Francisco, CA

Abstracts that were granted an exception in accordance with ASCO's Conflict of Interest Policy are designated with a caret symbol (^).

Abstract Disclosures

Abstract:

Background: Cabozantinib (cabo) inhibits MET and VEGFR2. High rates of bone scan resolution, pain relief and overall disease control, independent of PSA changes, were previously reported in a phase II study in mCRPC patients (pts). This is a NRE cohort in docetaxel (D)-pretreated pts with a novel primary endpoint of bone scan response based on computer-aided quantitative assessment of bone scan lesion area (BSLA) and a double-reader, independent, blinded review (Nucl Med Commun, in press). **Methods:** D-pretreated (≥225 mg/m^2) CRPC pts with bone metastasis were required to have progressed in soft-tissue or bone within 6 months of last dose of D. Pts received 100 mg cabo qd. Tumor response was assessed q6 wks. Bone scan response (BSR) was defined by a ≥30% decline in BSLA. Pain intensity (worst pain over the past 24 hrs; BPI scale 0-10) and interference with sleep and daily activity were prospectively assessed using an IVR system. Analgesic use was collected by diary. Bone turnover markers and CTCs were assessed. **Results:** 93 D-pretreated pts were enrolled (89 evaluable with ≥6 wks f/u). Median age was 67, 46% received cabazitaxel and/or abiraterone, 32% had visceral disease, 51% had fatigue, and 18% had anemia. 44% had worst pain ≥4 of which 95% were taking narcotics. Median CTC count was 49 and 80% had ≥5. Median f/u was 125 days (range, 23-305). Of 85 pts evaluable for BSR, 51 (60%) had a PR, 24 (28%) SD, 5 (6%) PD and 5 (6%) d/c'd prior to f/u scan. 21/30 pts (70%) had reduction of measurable disease.16/33 pts (49%) with BPI ≥4 and ≥12 wks f/u had pain reduction durable for ≥6 wks; 46% had decreased narcotic use, including 27% who discontinued use. Sleep and daily activity were improved in pts with pain relief. Among pts with elevated serum levels, 74%, 67% and 47% had declines on treatment of ≥30% in CTx, NTx and bALP, respectively. In 59 pts with CTCs ≥5, 92% had a decrease of ≥30% and 39% converted to <5 CTCs at weeks 6 or 12. 12% discontinued cabo due to AEs. Most common Gr 3/4 AEs were fatigue (19%), nausea (10%) and anemia (10%). **Conclusions:** Cabo treatment resulted in high rates of bone scan response, durable pain relief, and reductions in bone turnover markers and CTCs in D-pre-treated CRPC pts with bone metastases.

Appendix O

Safety and activity of the investigational agent orteronel (ortl) without prednisone in men with nonmetastatic castration-resistant prostate cancer (nmCRPC) and rising prostate-specific antigen (PSA): Updated results of a phase II study.

Subcategory:

Prostate Cancer

Category:

Genitourinary Cancer

Meeting:

2012 ASCO Annual Meeting

Session Type and Session Title:

Poster Discussion Session, Genitourinary (Prostate) Cancer

Abstract Number:

4549

Citation:

J Clin Oncol 30, 2012 (suppl; abstr 4549)

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Abstracts that were granted an exception in accordance with ASCO's Conflict of Interest Policy are designated with a caret symbol (^).

Abstract Disclosures

Abstract:

Background: Ortl is an investigational, oral, non-steroidal selective 17,20-lyase inhibitor that suppresses androgen production. Ortl affects cortisol synthesis less than similar agents due to limited inhibition of 17α-hydroxylase, and may permit steroid-free dosing. Ortl 300 mg BID was examined in patients (pts) with nmCRPC and rising PSA. **Methods:** Eligible pts had nmCRPC with PSA ≥2 ng/mL (PSA ≥8 ng/mL if doubling time >8 mo), and surgical/medical castration, with testosterone (T) <50 ng/dL. Prior chemotherapy, ketoconazole, or concomitant corticosteroids were excluded. Starting dose of ortl was 300 mg BID and continued until PSA progression, metastases, or unacceptable toxicity. The primary endpoint was the percentage of pts with PSA ≤0.2 ng/mL after 3 mo. Secondary endpoints included safety, PSA kinetics, time to metastases, changes in endocrine markers and circulating tumor cells (CTCs). **Results:** 39 pts were enrolled with baseline demographics including median age 71 y, ECOG PS ≤1, median PSA 12.1 ng/mL (range 2.6-67.8), T 7.9 ng/dL (1.4–17.3), and ACTH 19 ng/L (n=33; 0-47); 3 pts had dose reduction due to adverse events (AEs). Gr ≥3 AEs occurred in 16 pts (drug-related in 14); Gr ≥3 AEs ≥5% were dyspnea (8%), hypertension (13%), fatigue, hypokalemia, pneumonitis (5% ea). 7 pts (18%) had serious AEs; most common was pneumonitis (2=Gr 3, 1=Gr 2). 8 pts discontinued due to AEs; 2 pts required corticosteroids. At 3 mo, 6 pts (16%) achieved PSA ≤0.2 ng/mL; PSA50 and PSA90 rates were 76% and 32%, respectively; median PSA declined by 83% (n=34); median T declined by 89% to 0.78 ng/dL (n=31), and median ACTH increased by 171% to 43 ng/L; median cortisol declined by 21%. At 6 mo, PSA50 and PSA90 rates were 45% and 21%, respectively. Median time to PSA progression was 14.8 mo. 17 pts (44%) were on treatment >6 mo. Of 37 pts with baseline CTC/7.5 mL assessed, only 1 had CTC ≥5 and converted to <5; 6 had 1–4 CTCs at baseline, none converted to ≥5 during treatment. **Conclusions:** Ortl without steroids produces marked and durable declines in T and PSA, has manageable toxicities, and is feasible in men with nmCRPC.

Appendix P

Poster 100

A phase 2 multicenter study of the investigational single agent orteronel (TAK-700) in nonmetastatic castration-resistant prostate cancer (nmCRPC) and rising prostate-specific antigen (PSA)

Maha H. Hussain,[1] Paul G. Corn,[2] Dror Michaelson,[3] Hans J. Hammers,[4] Joshi J. Alumkal,[5] Charles J. Ryan,[6] Justine Y. Bruce,[7] Susan Moran,[8] Peter Mortimer,[9] Shih-Yuan Lee,[8] Daniel J. George[10]

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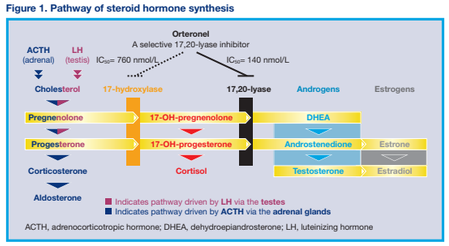
BACKGROUND

- Nonmetastatic, castration-resistant prostate cancer (nmCRPC) is an area of unmet medical need.[1-6]
  - One mechanism for castration resistance is the conversion of gonadal, adrenal, and tumoral androgen precursors to androgens, which results in tumor progression.[2-4]
- The only disease manifestation is rising prostate-specific antigen (PSA).[1]
- Median metastasis-free survival for patients with higher PSA values or shorter PSA doubling times is ~30 months.[1]
- Orteronel (TAK-700) is an investigational, selective, reversible, non-steroidal inhibitor of 17,20-lyase, a key enzyme in the production of steroidal hormones (Figure 1).
  - In preclinical studies, orteronel inhibited 17,20-lyase activity more than 17-hydroxylase, with IC_{50} values of 140 nmol/L (95% CI: 120, 170) and 760 (640, 910), respectively, with minimal effect on CYP drug-metabolizing enzymes.[7]
  - By comparison, corresponding IC_{50} values for abiraterone for human 17,20 lyase and 17-hydroxylase have been reported as 2.9 and 4.0 nmol/L, respectively.[8]
- Orteronel selectivity for 17,20-lyase may result in less effect on cortisol synthesis, reducing the potential for mineralocorticoid excess, and has potential to allow for steroid-free dosing, making orteronel an attractive drug for longer durations of therapy.
- This study evaluated a steroid-free regimen of orteronel, administered without regard to food, in patients with nmCRPC.

Figure 1. Pathway of steroid hormone synthesis



OBJECTIVES

Primary:

- The percentage of nmCRPC patients achieving a PSA reduction to ≤0.2 ng/mL (undetectable levels).

Secondary:

- Safety of orteronel
- PSA response rates at 3 and 6 months (decline in PSA of ≥90%, ≥50%, and/or ≥30%)
- Time to PSA progression, time to metastases, and duration of progression-free survival (PFS)
- Changes in endocrine markers: serum testosterone, ACTH, DHEA-S, LH, corticosterone, and cortisol concentrations.

Exploratory:

- Exploratory endpoints include analysis of circulating tumor cells (CTC)
- Other candidate biomarkers (not yet available).

METHODS

Key eligibility

Entry criteria:

- Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma without radiographic evidence of metastasis
- nmCRPC with progression as reflected by baseline PSA ≥2 ng/mL and high risk for metastases, based on a doubling time ≤8 months, or PSA ≥8 ng/mL with a doubling time >8 months
- ≥18 years of age
- Surgical or ongoing medical castration, with testosterone <50 ng/dL.

Exclusion criteria:

- Prior therapy with aminoglutethimide or ketoconazole
- Antiandrogen therapy within 4 weeks (flutamide) and 6 weeks (all others)
- Prior chemotherapy for prostate cancer other than in the adjuvant setting
- Radiation therapy for prostate cancer within 30 days prior.

Study design and treatment

- nmCRPC patients received orteronel without steroids at 300 mg twice daily (BID) in 28-day treatment cycles.
- Orteronel therapy was continued until PSA progression, metastases, or unacceptable toxicities.

Assessments

- Radiologic evaluations (CT/MRI) at screening assessed underlying disease status at study entry.
  - Evaluated at cycles 4, 7, 10, 13, and every 4th cycle thereafter until end of treatment.
- Toxicity according to NCI-CTCAE v4.03.
- Serum PSA levels.
- Adrenal function including plasma ACTH, serum cortisol, DHEA-S, LH, corticosterone, and testosterone.

Endpoint definitions

- Percent of nmCRPC patients achieving a PSA reduction to ≤0.2 ng/mL (undetectable levels).
- PSA progression: a 25% increase over the baseline/nadir concentration on two consecutive measurements at least 1 week apart and an absolute PSA increase of ≥2 ng/mL.
- PSA response rate: percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), or ≥30% (PSA30).
- PFS: time from first dose to first PSA progression, metastasis or death.
- Metastasis: ≥2 new lesions on bone imaging or 1 new lesion on soft tissue imaging.
- Time to metastasis: time from first dose to first occurence of metastasis.

Statistical considerations

Sample size

- 38 patients provided 90% power to give a 1-sided significance level of 0.1 (H_0 5% vs H_A 20%) for the percentage of patients achieving a PSA of ≤0.2 ng/mL after 3 months of orteronel treatment.

Population for analysis

- PSA response rate: patients with nmCRPC, PSA entry criteria, baseline and ≥1 post-baseline PSA measurement (N=38).
- Safety and time to event: patients with ≥1 dose of study drug (N=38).

Efficacy analysis

- Patients who achieve PSA of ≤0.2 ng/mL and had PSA assessments (PSA90, PSA50, PSA30).
- Time-to-event: Kaplan-Meier estimate of median time to event, and 6- and 12-month event-free probability.

RESULTS

- Data are presented as of January 25, 2013 and the study is currently ongoing.
- Patient demographics and disease characteristics are shown in Table 1.

Table 1. Baseline patient demographics

Characteristic	N=38
Median age, years (range)	71 (53–81)
Race (n, %)	
White	34 (89)
Black	4 (11)
ECOG performance status (n, %)	
0	32 (84)
1	6 (16)
Median (range)	
PSA	11.7 ng/mL (2.6–67.8)
Testosterone	8.5 ng/dL (1.4–17.3)
ACTH (n=32)	20 ng/L (0–47)

Safety

- Adverse events (AEs) were reported in 38 men (100%; Table 2).
- 12 patients discontinued due to AEs including 2 who discontinued treatment for grade 2 adrenal insufficiency; upon review of the data, only 1 patient had laboratory values consistent with a hypoadrenal state.

Table 2. Most common AEs irrespective of causality reported in ≥20% or grade 3/4 AEs in ≥5% of patients

	Orteronel 300 mg BID (N=38)			
AE, n (%)	All	Grade 1	Grade 2	Grade 3
Fatigue	25 (66)	15 (39)	8 (21)	2 (5)
Hypertension	17 (45)	2 (5)	8 (21)	7 (18)
Diarrhea	15 (39)	8 (21)	6 (16)	1 (3)
Nausea	13 (34)	12 (32)	1 (3)	0
Decreased appetite	12 (32)	9 (24)	3 (8)	0
Constipation	11 (29)	9 (24)	2 (5)	0
Dyspnea	10 (26)	7 (18)	0	3 (8)
Cough	9 (24)	9 (24)	0	0
Vomiting	9 (24)	8 (21)	1 (3)	0
Arthralgia	8 (21)	6 (16)	2 (5)	0
Dysgeusia	8 (21)	7 (18)	1 (3)	0
Dyspepsia	8 (21)	8 (21)	0	0
Hypokalemia	7 (18)	4 (11)	1 (3)	2 (5)
Pneumonitis	3 (8)	0	1 (3)	2 (5)
Syncope	2 (5)	0	0	2 (5)

Serious AEs were reported in 10 men (26%) which, in 6 men, were considered drug-related: 2 men had pneumonitis, 1 had pneumonitis, dyspnea, and hypoxia; 1 had syncope and atrioventricular block; 1 had atrial fibrillation and atrial flutter, and 1 had adrenal insufficiency. Grade 4 serious AEs were reported in 2 men and were considered unrelated to drug treatment: 1 with bladder cancer and humerus fracture and 1 with pulmonary embolism.

Treatment summary

- 27 men (71%) were on treatment for >6 months at the time of data cut-off.
- Median number of treatment cycles: 13 (range 1–27).
- Median therapy duration: 12.4 months (range 0.7–27.8) and 55% of patients were treated for >12 months.

Efficacy summary

PSA response

- 6 men (16%) achieved PSA ≤0.2 ng/mL at 3 months and 12 (32%) achieved PSA ≤0.2 ng/mL as their best response.
- 32% experienced a PSA90 at 3 months and 22 (58%) achieved PSA90 as their best response.
- 76% experienced a PSA50 at 3 months and 32 (84%) achieved PSA50 as their best response.
- PSA response rate at 3 and 6 months of treatment are summarized in Table 3.
- Waterfall plot of maximum PSA change at any time on treatment is shown in Figure 2.
- Waterfall plots of PSA change at 3 and 6 months are shown in Figure 3.

Table 3. PSA response rate at 3 and 6 months

	3 months		6 months		Best PSA response
N=38	n (%)	(80% exact CI)	n (%)	(80% exact CI)	
PSA ≤0.2ng/mL	6 (16)	(9, 26)	3 (8)	(3, 17)	12 (32)
PSA90	12 (32)	(22, 43)	9 (24)	(15, 35)	22 (58)
PSA50	29 (76)	(65, 85)	19 (50)	(39, 62)	32 (84)
PSA30	31 (82)	(71, 89)	22 (58)	(46, 69)	35 (92)

PSA response rate: percentage of patients achieving a decline in PSA of ≥90% (PSA90), ≥50% (PSA50), ≥30% (PSA30).

Figure 2. Waterfall plot of maximum PSA response at any time on treatment

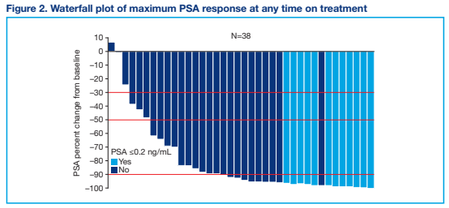
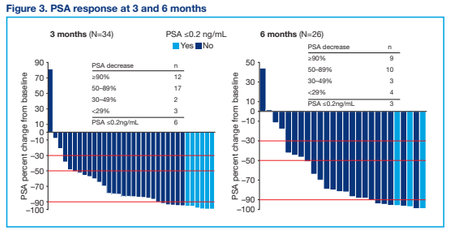


Figure 3. PSA response at 3 and 6 months



PSA progression

- Kaplan-Meier estimates of freedom from PSA progression were 88%, 57%, and 42% at 6, 12, and 24 months, respectively.
- Median time to PSA progression was 13.8 months (Figure 4).
- Duration of PSA response, as measured from time from first PSA response to protocol-defined PSA progression or death, is shown in Figure 5 for men who achieved PSA50 and PSA90 responses.

Figure 4. Kaplan-Meier time-to-PSA progression

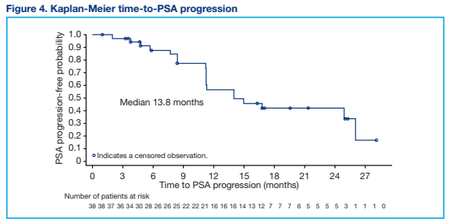
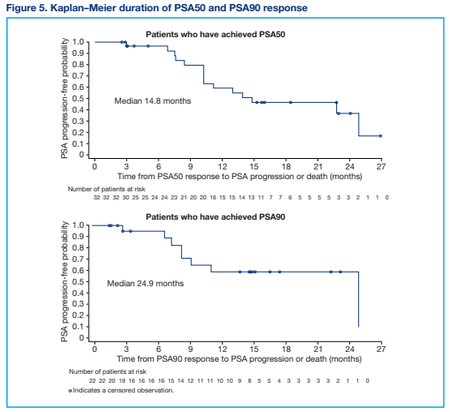


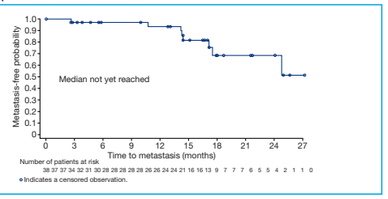
Figure 5. Kaplan–Meier duration of PSA50 and PSA90 response



Time to metastasis

- Kaplan-Meier estimates of freedom from metastasis was 94% and 69% for patients at 12 and 24 months, respectively (Figure 6).
  - 8 patients developed systemic metastasis after a median follow-up of 14.8 months.

Figure 6. Kaplan-Meier time to metastasis

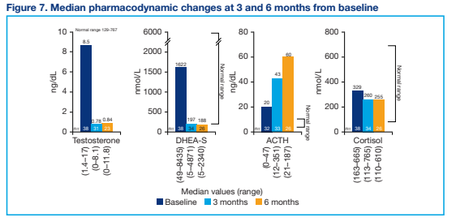


Endocrine markers

- Pharmacodynamic responses for serum testosterone, DHEA-S, ACTH, and cortisol are shown in Figure 7.
  - Testosterone decreased by 90% to median values of 0.78–0.84 ng/dL.*
  - DHEA-S decreased by 88% to median values of 188–197 nmol/L.
  - ACTH increased by ~2–3-fold to median values of 43–60 ng/dL.
  - Cortisol decreased by 21–23% to 255–260 nmol/L.

*Percent change from baseline is based on the number of patients with both baseline and post-baseline values at that cycle.

Figure 7. Median pharmacodynamic changes at 3 and 6 months from baseline



Circulating tumor cells

- 7 patients had ≥1 CTC at baseline assessment (Table 4).
  - 1 patient had ≥5 cells/7.5 mL at baseline and converted to <5 cells/7.5 mL at the 3, 6, and 12 month assessments.
  - No patients had ≥5 cells during orteronel treatment.

Table 4. CTC assessments

	Time of assessment			
	Baseline	3 months	6 months	12 months
Patients assessed (n)	35	33	23	18
Number of CTCs	**Patients with CTCs (n)**			
1–4 CTCs	6	2	2	2
≥5 CTCs	1	0	0	0

CONCLUSIONS

- In patients with nmCRPC and rising PSA, a steroid-free regimen of single-agent oral orteronel at a dose of 300 mg BID without prednisone and administered without regard to food, was feasible and had manageable toxicities.
  - The most common AEs were fatigue, nausea, and diarrhea (≥92% of each were grade 1/2), and hypertension (59% were grade 1/2).
  - There was an increase in ACTH levels outside the normal range, however the decreases in median cortisol levels were small and cortisol levels remained within the normal range.
  - Mineralocorticoid toxicities, such as hypertension and hypokalemia, were predominantly low grade and well managed without the use of steroids.
  - Although 2 patients discontinued treatment for "adrenal insufficiency", only 1 had laboratory values consistent with a hypoadrenal state for which he received corticosteroid replacement.
- 84% achieved ≥50% decrease in PSA and 32% achieved a PSA ≤0.2 ng/mL at any time on study.
  - After 3 months of orteronel treatment, 16% achieved PSA ≤0.2 ng/mL.
  - Median time to PSA progression was 13.8 months.
  - With a median follow up of 14.8 months, 8 patients developed systemic metastasis and freedom from metastasis was 94% and 69% for patients at 12 and 24 months, respectively.
  - Orteronel without prednisone suppressed adrenal androgens (testosterone and DHEA-S) by 85–89%.
    - Testosterone decreased from 8.5 ng/dL to 0.78–0.84 ng/dL and DHEA-S decreased from 1622 nmol/L to 197–188 nmol/L.

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The authors would like to thank the patients who participated in this study and their families, and the staff at all investigational sites.

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Disclosures

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Consultant or advisory role: DM (Millennium: The Takeda Oncology Company, Johnson & Johnson).
Research funding: MH, DM, DG (Millennium: The Takeda Oncology Company).
PC, HH, JA, CR, and JB have no conflicts to disclose.
Research was funded by Millennium: The Takeda Oncology Company.

Poster presented at the 28th Annual European Association of Urology (EAU) Congress, Milan, Italy, March 15–19, 2013. Abstract 2271.

Appendix Q

ASCO University
LIFELONG LEARNING

Safety, efficacy, and health-related quality of life (HRQoL) of the investigational single agent orteronel (ortl) in nonmetastatic castration-resistant prostate cancer (nmCRPC).

Subcategory:

Prostate Cancer

Category:

Genitourinary (Prostate) Cancer

Meeting:

2013 ASCO Annual Meeting

Session Type and Session Title:

General Poster Session, Genitourinary (Prostate) Cancer

Abstract Number:

5076

Citation:

J Clin Oncol 31, 2013 (suppl; abstr 5076)

Author(s):

Maha Hussain, Paul Gettys Corn, M Dror Michaelson, Hans J. Hammers, Joshi J. Alumkal, Charles J. Ryan, Justine Yang Bruce, Susan Moran, David MacLean, Shih-Yuan Lee, H. Mark Lin, Yanyan Zhu, Hongliang Shi, Peter Mortimer, Daniel J. George; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital Cancer Center, Boston, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Oregon Health & Science University Knight Cancer Institute, Portland, OR; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of Wisconsin Carbone Cancer Center, Madison, WI; Millennium Pharmaceuticals, Inc., Cambridge, MA; Takeda Global Research & Development Centre (Europe) Ltd., London, United Kingdom; Duke University Medical Center, Durham, NC

Abstracts that were granted an exception in accordance with ASCO's Conflict of Interest Policy are designated with a caret symbol (^).

Abstract Disclosures

2013 ASCO Annual Meeting Proceedings Errata
Abstract:

Background: Ortl is a selective, non-steroidal, oral 17,20-lyase inhibitor. Due to its lower inhibition of 17α-hydroxylase vs 17,20-lyase, ortl may allow steroid-free dosing. Ortl 300 mg BID was studied in nmCRPC patients (pts). **Methods:** Pts with nmCRPC, PSA ≥2 ng/mL (PSA ≥8 ng/mL if doubling time >8 mo), and testosterone (T) <50 ng/dL received ortl 300 mg BID until PSA progression, development of metastases (mets), or unacceptable toxicity. Primary endpoint: the percentage of pts with PSA ≤0.2 ng/mL at 3 mo. Secondary endpoints included safety, PSA kinetics, time to mets, and PFS (PSA progression, mets, or death), endocrine and bone markers, bone mineral density (BMD), HRQoL, cardiac and lipid assessments. **Results:** 38 pts enrolled: median PSA 11.7 ng/mL (range 2.6–67.8), T 8.5 ng/dL (1.4–17.3), and ACTH 20 ng/L (n=32; 0–47). Median therapy duration was 12.4 mo (0.7–27.8); 55% of pts were treated >12 mo. 6 had dose reduction, 12 discontinued due to adverse events (AEs), including 2 for possible adrenal insufficiency. Gr 3 hypertension occurred in 7 pts (18%); various ≥Gr 3 AEs occurred in another 14 pts; 10 pts (26%) had serious AEs. At 3 mo, median T declined 89% to 0.78 ng/dL; median ACTH increased 171%; median cortisol declined 21%, but remained within normal range. 97% of pts had PSA declines; median PSA declined 83%. 18% had PSA ≤0.2ng/mL at 3 mo; 32% achieved PSA ≤0.2ng/mL as best response. Median time to PSA progression was 13.8 mo. Median PFS was 13.8 mo. Kaplan-Meier estimates of 1 and 2 y mets-free rates were 94% and 69%, respectively; 8 pts developed mets on study. The patient-reported Aging Male Symptoms Scale showed no decrease in overall scores, psychological, somatic, or sexual domains in 37, 34, 25, and 19 pts assessed at visits 2, 4, 7, and 13, respectively. Serum lipids, cardiac assessments, HbA_{1C}, or bone-specific enzymes (N-telopeptide, or BMD) were not adversely affected. **Conclusions:** In pts with nmCRPC, long-term steroid-free ortl was feasible, with clinical activity as reflected by sustained marked declines in PSA and T, and had manageable toxicities, with no adverse effects on HRQoL, cardiac, bone or lipid profiles. Clinical trial information: **NCT01046916**.

Appendix R

ASCO University
LIFELONG LEARNING

A phase II trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC).

Subcategory:
Prostate Cancer

Category:
Genitourinary Cancer
Meeting:
2014 Genitourinary Cancers Symposium
Session Type and Session Title:
General Poster Session A: Prostate Cancer
Abstract Number:
83
Citation:
J Clin Oncol 32, 2014 (suppl 4; abstr 83)
Author(s):
Daniel Peter Petrylak, David C. Smith, Leonard Joseph Appleman, Mark T. Fleming, Arif Hussain, Robert Dreicer, A. Oliver Sartor, Neal D. Shore, Nicholas J. Vogelzang, Hagop Youssoufian, William C. Olson, Nancy Stambler, Kathleen Huang, Robert Joseph Israel; Yale University Medical Center, New Haven, CT; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; University of Pittsburgh, Pittsburgh, PA; US Oncology Research, The Woodlands, TX; Virginia Oncology Associates, Hampton, VA; University of Maryland Cancer Center, Baltimore, MD; Cleveland Clinic, Cleveland, OH; Tulane Cancer Center, New Orleans, LA; Carolina Urologic Research Center, Atlantic Urology Clinics, Myrtle Beach, SC; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Progenics Pharmaceuticals, Inc., Tarrytown, NY

Abstract Disclosures

2014 Genitourinary Cancers Symposium Proceedings Errata

Abstract:

Background: The abundant expression of prostate-specific membrane antigen (PSMA) on prostate cancer cells provides a rationale for antibody therapy. PSMA antibody drug conjugate (ADC) is a fully human antibody to PSMA linked to the microtubule disrupting agent monomethyl auristatin E (MMAE). It binds PSMA and is internalized and cleaved by lysosomal enzymes releasing free MMAE causing cell cycle arrest and apoptosis. We enrolled 70 patients (pts) in a phase II trial of PSMA ADC in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC). **Methods:** Pts with progressive mCRPC following taxane and ECOG PS 0 or 1 were eligible. PSMA ADC was administered Q3 week IV for up to eight cycles. Safety, tumor response by prostate-specific antigen (PSA), circulating tumor cells (CTC), imaging, biomarkers and clinical progression were assessed. Dosing was initiated at 2.5 mg/kg and adjustment for tolerability was allowed. **Results:** Thirty five pts began treatment at 2.5 mg/kg. Due to neutropenia, the remaining 35 pts began at 2.3 mg/kg. All pts received prior docetaxel and abiraterone and/or enzalutamide. Forty one percent also received cabazitaxel. Adverse events (AEs) were consistent with what was seen in phase I; most common

significant AEs were neutropenia (grade 4, 6.7% and 11.4% at 2.3 and 2.5 mg/kg, respectively) and peripheral neuropathy (grade 3 or higher, 6.7% (2.3) and 5.7% (2.5)). Two pts at 2.5 mg/kg died of sepsis. 43% of pts at 2.3 and 37% of pts at 2.5 had declines in CTC from 5 or more to less than 5 cells/7.5 ml blood and 57.1% (2.3) and 74.1% (2.5) had 50% or more CTC declines; 26.1% (2.3) and 16.1% (2.5) had PSA declines of 30% or more thus far. PSA and CTC responses were associated with higher PSMA expression on CTC and lower neuroendocrine (NE) markers. The CTC conversion rate (5 or more to less than 5) was approximately 80% in pts with low NE markers. Prior cabazitaxel or abiraterone and/or enzalutamide did not appear to affect response. Centralized assessments of images by RECIST of all pts are currently planned and will be presented.
Conclusions: PSMA ADC at 2.3 mg/kg was generally well tolerated in pts with progressive mCRPC previously treated with taxane. Anti-tumor activity, CTC and PSA reductions were observed at 2.3 and 2.5 mg/kg. Updated safety, tumor response and radiographic assessments from the full cohorts of 2.3 and 2.5 mg/kg will be presented. Testing in taxane naïve pts is also ongoing. Clinical trial information: **NCT01695044**

Appendix S

Meeting Abstracts

Concordance of ETS fusion status of matched metastatic castration-resistant prostate cancer and primary prostate cancer: Data from NCI 9012, a randomized ETS fusion-stratified phase II trial.

Sub-category:
Prostate Cancer

Category:
Genitourinary (Prostate) Cancer

Meeting:
2014 ASCO Annual Meeting

Abstract No:
5019

Type: Poster Highlights Session

Author(s): Lakshmi Priya Kunju, Nallasivam Palanisamy, Stephanie Daignault, Rohit Mehra, Javed Siddiqui, Shannon Lea Carskadon, Przemyslaw Twardowski, Mark N. Stein, Noah M. Hahn, Walter Michael Stadler, Jon Jacobson, Matthew S. Davenport, Scott A. Tomlins, Arul M. Chinnaiyan, Felix Yi-Chung Feng, Maha Hussain; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Michigan Center for Translational Pathology, University of Michigan, Ann Arbor, MI; University of Michigan Medical Center, Ann Arbor, MI; University of Michigan Center for Translational Pathology, Ann Arbor, MI; City of Hope, Duarte, CA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; The University of Chicago Medicine and Biological Sciences, Chicago, IL; Department of Pathology, University of Michigan Medical School, Ann Arbor, MI; University of Michigan Health System, Ann Arbor, MI

Abstract Disclosures

Abstract:

Background: Fusions of androgen-regulated genes with ETS transcription family members have been reported in 50% of localized pPCa patients (pts), with *TMPRSS2-ERG* fusions being the

most common. ETS fusion products functionally depend upon Poly (ADP-ribose) polymerase 1 (PARP1), and its inhibition is preferentially cytotoxic to ETS translocation positive disease in preclinical models. We hypothesized that targeting ETS gene fusions will improve response rate in pts with these molecular subtypes and in pts with ETS fusion positive tumors, targeting the promoter and transcription factor of ETS fusion is more effective than targeting a single aspect of the fusion. **Methods:** Eligible mCRPC pts undergo a metastatic site biopsy to determine ETS fusion status by immunohistochemistry (ERG), fluorescent in-situ hybridization and/or RNA in-situ hybridization (ETV1) and sequencing (ETV4). Pts are stratified by ETS status and randomized to abiraterone (ABI) +/- the PARP inhibitor veliparib. Soft tissue biopsies are done using 18-gauge needle: 1-cm core (≥ 6 specimens), 2-cm core (≥4 specimens). For bone biopsy: 2-8 cores. We report interim results on rates of positive biopsy, ETS status/type and concordance between primary PCa and metastasis. **Results:** To date, 86 pts (Caucasians: 80%, African Americans 14%) with a median age 70 years and a median PSA 36.3 ng/ml have been enrolled. Of the 86 pts, 1 had an unreachable bone lesion, 36 had soft tissue and 49 had bone biopsies; all soft tissue and 36/49 (73%) bone biopsies were evaluable for analysis (13 had no tumor), ETS fusion status is positive in 36% pts: ERG positive (31%), ETV1 positive (4%), ETV4 positive (1%). Concordance of ETS status between primary PCa and metastatic site was found in 30/31 pts (97 % [95% CI: 83-99.9%]. **Conclusions:** This trial represents one of the first prospective predictive biomarker-driven trials in mCRPC. Results indicate feasibility of real time biopsy (adequate tissue yield including from bone) and biomarker determination, and demonstrates significant concordance of ETS status between primary PCa and metastasis in the subset analyzed to date. Clinical trial information: NCT01576172.

Appendix T

Meeting Abstracts

A phase 2 trial of prostate-specific membrane antigen antibody drug conjugate (PSMA ADC) in taxane-refractory metastatic castration-resistant prostate cancer (mCRPC).

Sub-category:
Prostate Cancer

Category:
Genitourinary (Prostate) Cancer

Type: Poster Highlights Session

Meeting:
2014 ASCO Annual Meeting

Abstract No:
5023

Author(s): Daniel Peter Petrylak, David C. Smith, Leonard Joseph Appleman, Mark T. Fleming, Arif Hussain, Robert Dreicer, A. Oliver Sartor, Neal D. Shore, Nicholas J. Vogelzang, Hagop Youssoufian, Vincent A. DiPippo, Nancy Stambler, Kathleen Huang, Robert Joseph Israel; Yale University Medical Center, New Haven, CT; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; University of Pittsburgh Medical Center, Pittsburgh, PA; US Oncology Research; Virginia Oncology Associates, Hampton, VA; University of Maryland Cancer Center, Baltimore, MD; Cleveland Clinic, Cleveland, OH; Tulane University, New Orleans, LA; Carolina Urologic Research Center, Atlantic Urology Clinics, Myrtle Beach, SC; Comprehensive Cancer Centers of Nevada, Las Vegas, NV; Progenics Pharmaceuticals, Inc., Tarrytown, NY

Abstract Disclosures

Abstract:

Background: PSMA expression on prostate cancer cells provides a rationale for ADC therapy. PSMA is a clinically validated target. PSMA ADC is a fully human antibody to PSMA linked to the microtubule disrupting agent MMAE. It induces cell cycle arrest and apoptosis specifically in PSMA-positive cells. We have completed enrollment in a multicenter phase 2 trial of PSMA ADC in mCRPC pts progressing after taxane and antiandrogen. Methods: Pts with progressive

mCRPC following taxane and abiraterone (ABI) and/or enzalutamide (ENZ) regimens and ECOG PS 0, 1 or 2 were eligible. PSMA ADC was administered Q3 wk IV for up to 8 cycles. Safety, tumor response by PSA, circulating tumor cells (CTC), imaging, biomarkers and clinical progression were assessed. Dosing was initiated at 2.5 mg/kg and adjusted for tolerability. Results: 34 pts received PSMA ADC at 2.5 mg/kg. Due to neutropenia, 49 pts subsequently received 2.3 mg/kg. 39% had both docetaxel and cabazitaxel (CAB); and 58% had both ABI and ENZ. 30% had visceral or soft tissue metastases. Duration of therapy on 2.3 mg/kg was longer than on 2.5 mg/kg. Any related adverse event (AE) grade ≥3 was 37% (2.3) and 59% (2.5 mg/kg). Related, grade 3/4 AEs occurring in ≥10% were fatigue, neutropenia and decreased electrolytes (16% vs 15%, 6% vs 18%, and 8% vs 21% at 2.3 and 2.5 mg/kg, respectively). 2 pts at 2.5 mg/kg died of sepsis. PSA decline of ≥30% was noted in 36% (2.3) and 16% (2.5 mg/kg), and CTC decline of ≥50% was noted in 74% pts in both 2.3 and 2.5 mg/kg. CTC conversion from ≥5 to <5 cells/7.5 ml blood occurred in 48% (2.3) and 50% (2.5 mg/kg). PSA and CTC responses were associated with higher PSMA+CTC and PSA responses with lower neuroendocrine markers. Stable disease was seen in 80% of RECIST evaluable pts (n=15). Pts with prior CAB had lower CTC responses. Responses in pts with prior ABI did not differ from pts with prior ENZ. Conclusions: PSMA ADC at 2.3 mg/kg was active and well tolerated in heavily pretreated mCRPC pts. Updated safety and secondary efficacy endpoints from the 2.3 and 2.5 mg/kg cohorts will be presented. These data warrant further evaluation in this population. A taxane-naïve cohort is ongoing. Clinical trial information: NCT02020135.

Appendix U

Meeting Abstracts

Primary outcomes of the placebo-controlled phase 2 study PERSEUS (NCT01360840) investigating two dose regimens of abituzumab (DI17E6, EMD 525797) in the treatment of chemotherapy-naive patients (pts) with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC).

Sub-category:
Prostate Cancer

Category:
Genitourinary (Prostate) Cancer

Type: Poster Highlights Session

Meeting:
2014 ASCO Annual Meeting

Abstract No:
5030

Author(s): Maha Hussain, Kurt Miller, Ilona Rybicka, Rolf Bruns; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Charité, Department of Urology, Berlin, Germany; Merck KGaA, Darmstadt, Germany

Abstract Disclosures

Abstract:

Background: The humanized monoclonal IgG2 antibody abituzumab inhibits αv integrins expressed on CRPC cells, tumor vessels, and osteoclasts involved in bone (B) metastasis. It showed antitumor effects in in vivo CRPC models and was well tolerated in a phase 1 study in mCRPC pts previously treated with docetaxel. Methods: PERSEUS is an exploratory double-blind trial with 180 pts randomized 1:1:1 to placebo, abituzumab 750, or 1,500 mg i.v. given every 3 weeks in addition to standard of care. Eligible pts had radiologic disease progression (rPD) of B lesions <28 days prior to randomization. Pts were treated until rPD in either B or soft tissue (ST) lesions, skeletal event, death, or unacceptable toxicity. Primary endpoint was progression-free survival (PFS). In addition, overall response (OR, RECIST 1.0) and safety were

assessed. Results: Baseline characteristics were balanced across arms. In pts treated with placebo, abituzumab 750, and 1500 mg, median PFS (ITT) was 3.3 (95% CI: 2.8, 4.8), 3.4 (95% CI: 2.8, 5.6; HR = 0.89 [95% CI: 0.57, 1.39]), and 4.3 months (95% CI: 2.8, 6.6; HR = 0.81 [95% CI: 0.52, 1.26]), respectively. Progression occurred in 72, 68, and 65% of pts, respectively, incl. B lesion progression observed in 42% of pts in the control arm and in 23% of pts in each abituzumab arm. Of 74 OR-evaluable pts with confirmed ST lesions at baseline, 2 achieved partial responses (placebo: 1/28 pts; abituzumab 1500 mg: 1/24 pts). Treatment-emergent adverse events (TEAEs) occurred in 92, 85, and 88% of pts in the placebo, abituzumab 750, and 1500 mg arms, respectively, incl. serious TEAEs in 27, 22, and 23% and TEAEs with fatal outcomes in 3, 3, and 5% (treatment-related AE: 1 pt in the placebo arm). Conclusions: Median PFS with abituzumab 1500 mg was above the duration observed with 750 mg or placebo. Compared with placebo, pts receiving abituzumab experienced B progression less frequently. Considering these favorable trends, further investigation of abituzumab efficacy is needed. Its previously observed safety profile was confirmed. Clinical trial information: NCT01360840.

Appendix V

Meeting Abstracts

Comprehensive molecular profiling of pretreatment metastatic castration resistant prostate cancer (CRPC): Secondary data from NCI 9012, a randomized ETS fusion-stratified phase II trial.

Sub-category:
Prostate Cancer

Category:
Genitourinary (Prostate) Cancer

Meeting:
2014 ASCO Annual Meeting

Abstract No:
e16038

Author(s): Scott A. Tomlins, Dan Robinson, Yi-Mi Wu, Robert J Lonigro, Pankaj Vats, Shanker Kalyana Sundaram, Xuhong Cao, Lakshmi Priya Kunju, Nallasivam Palanisamy, Stephanie Daignault, Rohit Mehra, Javed Siddiqui, Arul M. Chinnaiyan, Felix Yi-Chung Feng, Maha Hussain; Department of Pathology, University of Michigan Medical School, Ann Arbor, MI; Center for Translational Pathology, University of Michigan, Ann Arbor, MI; Pathology Department, University of Michigan, Ann Arbor, MI; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Michigan Center for Translational Pathology, University of Michigan, Ann Arbor, MI; University of Michigan Medical Center, Ann Arbor, MI; University of Michigan Health System, Ann Arbor, MI

Abstract Disclosures

Abstract:

Background: Robust molecular subtypes have been identified in castration resistant prostate cancers (CRPC), including those that harbor ETS gene fusions. Preclinical studies suggest that tumors harboring ETS fusions are preferentially sensitive to poly (ADP-ribose) polymerase 1 (PARP1) inhibition. A multi-institutional phase II trial of abiraterone (ABI) +/- the PARP inhibitor veliparib in men with CRPC is assessing the utility of ETS fusion status from metastatic tumor biopsies as a predictive biomarker. In addition, when additional tissue is obtained, we are

performing comprehensive molecular profiling through the Mi-Oncoseq initiative. Here we report molecular profiles of response extremes. **Methods:** Eligible mCRPC pts undergo a metastatic site biopsy to determine ETS fusion status by FISH and/or ISH. Additional tissue is fresh frozen and used for exome and transcriptome sequencing and comprehensive analysis through the Mi-Onocseq pipeline. **Results:** To date, 86 patients have been enrolled. Of the 86 patients, 12 had sufficient tissue to perform Mi-Oncoseq molecular profiling. Patient 43 (ETS fusion negative, serum PSA 113ng/mL at enrollment) presented with hepatic and nodal metastases and has had radiographic response and achieved undetecatble PSA while on study. Profiling of a pre-study hepatic tumor sample demonstrated an *AR* 875Y somatic mutation, a low-level *AR* amplification, and a homozygous, somatic deletion of *BRCA2*. Patient 26 (ETS fusion positive, serum PSA 3.1ng/mL at enrollment) presented with a bladder recurrence/metastasis and rapidly progressed while on study. Profiling of a pre-study bladder resection specimen demonstrated a *TMPRSS2:ERG* gene fusion, high level *MDM4* amplification, homozygous deletions of *PTEN*, *KDM5A* and *RB1*, and very high expression of proliferation related genes. Additional molecular data on other pts will be presented. **Conclusions:** Comprehensive, real-time molecular profiling of CRPC is feasible. Point mutations/indels, copy number alterations, gene fusions and transcriptional profiles can be identified and associated with treatment response. Clinical trial information: NCT01576172.

Original Article

Vorinostat in Advanced Prostate Cancer Patients Progressing on Prior Chemotherapy (National Cancer Institute Trial 6862)

Trial Results and Interleukin-6 Analysis: A study by the Department of Defense Prostate Cancer Clinical Trial Consortium and University of Chicago Phase 2 Consortium

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BACKGROUND: This phase 2 trial was designed to evaluate the efficacy of vorinostat in chemotherapy-pretreated patients with metastatic castration-resistant prostate cancer. **METHODS:** Patients with disease progression on 1 prior chemotherapy, a prostate-specific antigen (PSA) $\geq$5 ng/mL, and adequate organ function were treated with 400 mg vorinostat orally daily. The primary endpoint was the 6-month progression rate. Secondary endpoints included safety, rate of PSA decline, objective response, overall survival, and effects of vorinostat on serum interleukin-6 (IL-6) levels. **RESULTS:** Twenty-seven eligible patients were accrued. The median number of cycles delivered was 2 (range, 1-7). All patients were taken off therapy before 6 months. The best objective response in the eligible patient was stable disease in 2 (7%) patients. No PSA decline of $\geq$50% was observed. There was 1 grade 4 adverse event (AE), and 44% of patients experienced grade 3 adverse events. The most common adverse events were fatigue (81%), nausea (74%), anorexia (59%), vomiting (33%), diarrhea (33%), and weight loss (26%). Median time to progression and overall survival were 2.8 and 11.7 months, respectively. Median IL-6 levels (pg/mL) were higher in patients removed from the protocol for toxicity compared with progression at all time points, including baseline (5.2 vs 2.1, P=.02), Day 15 Cycle 1 (9.5 vs 2.2, P=.01), Day 1 Cycle 2 (9.8 vs 2.2, P=.01), and end of study (11.0 vs 2.9, P=.09). **CONCLUSIONS:** Vorinostat at this dose was associated with significant toxicities limiting efficacy assessment in this patient population. The significant association between IL-6 levels and removal from the study for toxicities warrants further investigation. **Cancer 2009;115:5541–9. © 2009 American Cancer Society.**

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With the establishment of docetaxel as standard first-line chemotherapy for castration-resistant prostate cancer,[1,2] a clinical research priority in this disease is to identify second-line therapy. Histone deacetylases regulate cell signaling and gene transcription through removal of acetyl groups from histone and nonhistone proteins.[3-5] Inhibition of histone deacetylase activity leads to accumulation of acetylated proteins, which in turn lead to alterations in transcription, mitosis, and protein stability, with resultant inhibition of tumor cell proliferation and survival.[3-6] In preclinical studies, histone deacetylase inhibitors have been shown to induce tumor cell cytostasis, differentiation, and apoptosis, and to inhibit tumor angiogenesis in various hematologic and solid malignancies. In prostate cancer, histone deacetylase inhibition has resulted in decreased proliferation in cell lines,[7-9] and decreased tumor growth in preclinical models,[9-15] suggesting that histone deacetylase inhibition is of potential therapeutic benefit in this disease.

Vorinostat is a small molecule inhibitor of class I and II histone deacetylases that has been approved by the Food and Drug Administration for treatment of cutaneous T-cell lymphoma.[16-18] In early testing, vorinostat showed significant antitumor activity in a broad range of cancers,[19-22] including preclinical activity in prostate cancer.[23,24] Specifically, vorinostat suppressed the growth of the LNCaP, PC-3, and TSU-Pr1 cell lines at micromolar concentrations.[23] In mice with transplanted CWR222 human prostate tumors, vorinostat treatment at 50 mg/kg/day resulted in significant suppression of tumor growth. At this dose, there was no detectable toxicity, as evaluated by change in weight and necropsy examination.[23] Kulp and colleagues have similarly shown growth inhibition of PC-3, DU-145, and LNCaP human prostate cancer cell lines and suppression of PC-3 xenograft tumors with vorinostat treatment.[9] These biologic, preclinical, and phase 1 data collectively provided the rationale for testing vorinostat in patients with castration-resistant prostate cancer failing prior chemotherapy.

Interleukin-6 (IL-6) is a pleiotropic cytokine that stimulates the progression of a variety of cancers. Multiple studies have demonstrated that IL-6 is elevated in the sera of patients with metastatic prostate cancer.[25-27] Drachenberg and colleagues[28] reported elevated serum IL-6 levels in men with hormone-refractory prostate cancer compared with normal controls, benign prostatic hyperplasia, prostatitis, and localized or recurrent disease, suggesting that IL-6 may be a surrogate marker of the androgen-independent phenotype. IL-6 has also been associated with disease progression and has been implicated as a potential marker of response to therapy.[29-31] Histone deacetylase inhibition has also been shown to be associated with decreased expression of IL-6 and other proinflammatory mediators.[32-34] These findings, along with the observations that vorinostat can down-regulate the IL-6 signaling cascade,[35] portend a possible role for the evaluation of IL-6 as an indicator of response to vorinostat. We hypothesized that vorinostat-mediated down-regulation of IL-6 activity would be associated with a favorable outcome.

MATERIALS AND METHODS

This Cancer Therapy Evaluation Program-sponsored trial was conducted by the Department of Defense Prostate Cancer Clinical Trials Consortium and the National Cancer Institute (NCI)-sponsored University of Chicago Phase 2 Consortium. The protocol was reviewed and approved by the institutional review board at each participating institution, and all patients provided informed consent before initiation of any study procedures. Eligible patients had metastatic prostate cancer with measurable and/or bony disease that had progressed despite androgen deprivation therapy and 1 prior chemotherapy regimen for castration-resistant prostate cancer. All patients were required to have prostate-specific antigen (PSA) progression defined as at least 2 rises in PSA documented over a reference value, no less than 7 days apart, with a minimum value of 5 ng/mL. Patients had to have an Eastern Oncology Cooperative Group performance status of

0-2 and adequate hematological, renal, and hepatic function defined by a white blood count of $\geq$3000/μL, absolute neutrophil count $\geq$1500/μL, platelet count $\geq$100,000/μL, creatinine <2mg/dL, bilirubin within normal limits, and aspartate aminotransferase and alanine transaminase $\leq$2.5$\times$ the upper limits of normal. Patients with significant cardiovascular disease including congestive heart failure (New York Heart Association class III or IV), active angina pectoris, or recent myocardial infarction (within the last 6 months) were excluded. Patients requiring diuretics for reasons other than hypertension, digoxin for reasons other than atrial fibrillation, or with a history of mild to moderate congestive heart failure, or patients with electrocardiogram results of 1) significant q waves, 2) ST elevation or depressions of >2 mm, 3) the absence of a regular sinus rhythm, or 4) the presence of a bundle block were required to undergo additional cardiac testing. Patients with known brain metastases were excluded, but those with treated and controlled epidural disease were eligible. Patients on luteinizing hormone-releasing hormone (LHRH) agonists were required to continue therapy. Discontinuation of all nonsteroidal antiandrogens (28 days for flutamide and 42 days for bicalutamide) was required. Patients taking valproic acid (a histone deacetylase inhibitor) must have stopped therapy at least 2 weeks before registration. No investigational or commercial agents (other than LHRH analogues) or therapies including other hormonal agents such as steroids, megesterol acetate (unless low dose given for hot flashes), antiandrogens, or herbal medications were permitted to be administered with the intent to treat the patient's malignancy. Patients with a currently active second malignancy other than nonmelanoma skin cancers were not eligible. Patients were not considered to have a currently active malignancy if they had completed therapy and were considered by their physician to show no evidence of disease.

Treatment Plan

Patients received open-label oral vorinostat 400 mg daily continuously. All patients completed a medication diary to monitor compliance. Toxicity was assessed using NCI Common Toxicity Criteria for Adverse Events version 3.0, and dose reductions to 300 mg/day and 100 mg/day were specified for grade 3 or 4 toxicities. Patients were evaluated clinically and by laboratory tests every 21 days. A maximum 4-week break in treatment for toxicity resolution was permitted.

Duration of Therapy, Monitoring, and Response Assessment

Patients were monitored by history and physical exam, toxicity assessment, and PSA every 3 weeks. Response assessment by bone scan and computed tomography scan and/or other appropriate imaging was performed every 12 weeks. Patients were removed from the protocol if there was evidence of progression by PSA or Response Evaluation Criteria in Solid Tumors criteria, or symptomatic progression. Patients with progression by bone scan only at first assessment continued treatment with reassessment after 6 additional weeks of therapy. Patients with confirmed progression were removed from the protocol. Patients with stable disease or better were permitted to continue protocol therapy. Patients demonstrating progression by bone scan or other measures at the 24-week or subsequent scheduled assessments were considered as having progressive disease, and a confirmation of progression was not required. All patients were followed for survival.

Response and Progression Definition

Progression for the purpose of the study was defined by any 1 or more of the following parameters: 1) PSA progression—25% increase over baseline or nadir, whichever is lower, and an increase in the absolute value of PSA by 5 ng/mL that is confirmed by another PSA at no less than a 4-week interval; 2) measurable disease progression—progression of target lesions by Response Evaluation Criteria in Solid Tumors criteria[36]; 3) nonmeasurable disease progression—worsening of bone scan defined as development of $\geq$2 new lesions, appearance of new metastatic lesions outside of the bone, unequivocal progression of existing nontarget lesions, or development of an indication for radiation therapy or other change in cancer therapy based on a change in a disease manifestation while on therapy.

Objective responses were defined using Response Evaluation Criteria in Solid Tumors criteria.[36] PSA response was defined based on the PSA Working Group Consensus Criteria.[37] Bone disease was evaluated by bone

Table 1. Patient Characteristics, N = 27

Characteristic	No. of Patients
Age, median y (range)	68 (54-80)
Race	
White	21 (78%)
Nonwhite	6 (22%)
Performance status	
0	7 (26%)
1	19 (70%)
2	1 (4%)
PSA, median ng/mL (range)	95 (5.8-1526)
Disease progression at registration	
PSA	100%
Soft tissue	56%
Bone	81%
Prior chemotherapy for CRPC	
Docetaxel	25 (92%)
Paclitaxel	1 (4%)
Cyclophosphamide	1 (4%)

PSA indicates prostate-specific antigen; CRPC, castration-resistant prostate cancer.
Two patients were ineligible (total 29 patients registered). Patients were registered between May 2006 and February 2007.

scan, with disease characterized as complete response if there was disappearance of all osseous lesions as evaluated by scans, stable or improved if there were no new lesions and no new pain in an area where uptake was previously observed, and progression if there was the appearance of 2 or more new skeletal lesions. An increase in the size or intensity of lesions was not considered progression.

Endpoints and Statistical Design

The primary objective of this phase 2 trial was to evaluate the activity of oral vorinostat in patients with metastatic prostate cancer that had progressed on 1 prior chemotherapy regimen. The primary endpoint was the proportion of patients who did not demonstrate disease progression at 6 months. On the basis of a published retrospective analysis of second-line chemotherapy in men with metastatic castration-resistant prostate cancer,[38] the expected progression rate by criteria used in this protocol in this patient population at 6 months is 84% (nonprogression rate of 16%). Therefore, if the progression-free rate was 10% or less, there would be little interest in pursuing this therapy further, whereas with a progression-free rate of 30% or more, further study would be proposed.

Given the late time point for measuring progression, a single-stage design was used. By using Fisher exact test, 29 patients were to be accrued. If 7 or more of these 29 patients were progression-free at 6 months, this agent would be felt to be worthy of further evaluation. This design provided for 80% power at the 5% significance level.

Secondary endpoints were to evaluate the safety of vorinostat and to determine the objective response rate in patients with bidimensionally measurable disease, the rate of PSA decline of $\geq$50%, and progression-free and overall survival.

Correlative Biology Studies

When designing this trial, we hypothesized that vorinostat-mediated down-regulation of IL-6 activity would be associated with a favorable outcome. However, because all eligible patients were taken off the study before 6 months, this analysis was not possible. Given that IL-6 is associated with the systemic immune response,[39] we performed an exploratory analysis to determine whether patients with higher levels of serum IL-6 were more likely to be removed from the protocol for toxicity versus progression.

Pretreatment and on-treatment peripheral blood samples for IL-6 were collected 2 hours after the most recent dose of vorinostat on Day 15 of Cycle 1, Day 1 of Cycle 2, the last week of Cycle 4, and at the time of removal from the study. Quantitative levels of IL-6 were measured using a human IL-6 immunoassay (Quantikine HS, R&D Systems, Minneapolis, Minn) according to the manufacturer's instructions. IL-6 levels were compared between patients removed from the protocol for progression versus toxicity using the Wilcoxon rank sum test.

RESULTS

Between May 2006 and February 2007, 29 patients were registered to the protocol. Two patients were ineligible (because of noncastration testosterone levels or previous treatment with a radiopharmaceutical). Table 1 lists baseline patient characteristics of the 27 eligible patients. The median age was 68 years (range, 54-80 years). Seventy percent of patients had a performance status of 1. Previous chemotherapy treatment for metastatic castration-resistant prostate cancer included docetaxel (92%),

Table 2. Treatment-Related Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue (81%)	7	8	7	0
Nausea (74%)	11	7	2	0
Anorexia (59%)	5	8	3	0
Diarrhea (33%)	9	0	0	0
Vomiting (33%)	8	0	1	0
Dehydration (26%)	4	3	0	0
Weight loss (26%)	7	0	0	0
↓ Platelet count (22%)	4	1	1	0
Taste alteration (22%)	4	2	0	0
↑ Creatinine (19%)	2	3	0	0
Dry mouth (15%)	3	1	0	0
Leukopenia (15%)	3	1	0	0
Urinary frequency (15%)	4	0	0	0
↑ AST (11%)	2	1	0	0
Edema limbs (11%)	3	0	0	0
↓ Hemoglobin (11%)	1	1	1	0
Mucositis oral (11%)	2	1	0	0
Muscle weakness (11%)	3	0	0	0
Thrombosis*	0	0	0	1
Hematuria*	0	0	1	0
Abdominal pain*	0	0	1	0
Pain*	0	0	1	0

AST indicates aspartate aminotransferase.
Grades are based on the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.
* All grade 3 and 4 treatment-related adverse events are listed.

paclitaxel (4%), and cyclophosphamide (4%). All patients are off protocol therapy, with a median number of cycles given of 2 (range, 1-7). Seventy percent of patients required dose reduction.

Adverse Events

Forty-eight percent of patients experienced grade 3 or 4 toxicities. There were no grade 5 (treatment-related deaths) adverse events. Table 2 describes in detail toxicities by type and grade, for which 70% of patients required dose reductions. The most common adverse events were fatigue (81%), nausea (74%), anorexia (59%), vomiting (33%), diarrhea (33%), and weight loss (26%). Eleven (41%) patients discontinued therapy because of toxicity (Table 3).

Response and Survival

All eligible patients were off therapy before 6 months (Table 3);13 (48%) were removed because of progression, 11 (41%) secondary to toxicity, and 3 (11%) for other reasons. The best objective response obtained was stable disease in 2 patients (7%). Duration of stable disease was 84 and 135 days, respectively. No PSA declines of $\geq$50% were observed (Fig. 1). Median time to progression was 2.8 months (range, 0.5-5.3 months), with a median overall survival of 11.7 months (2.3-14 months, with 1 patient censored at 15.1 months). Of note, the 2 additional ineligible patients not included in the final analysis also achieved a best objective response of stable disease.

Correlative Studies

Median IL-6 levels (pg/mL) were higher in patients removed from the protocol for toxicity versus progression at all time points, including baseline (5.2 vs 2.1, $P = .02$), Day 15 Cycle 1 (9.5 vs 2.2, $P = .01$), Day 1 Cycle 2 (9.8 vs 2.2, $P = .01$), and end of study (11.0 vs 2.9, $P = .09$) (Fig. 2).

DISCUSSION

To date there is no established second-line systemic therapy for patients with castration-resistant prostate cancer. Histone deacetylase inhibitors are attractive agents, particularly in prostate cancer, because of a demonstrated effect in vitro on proliferation, differentiation, apoptosis, and angiogenesis coupled with antitumor effects in preclinical prostate cancer models.

Table 3. Treatment Discontinuation by Cycle, N = 27

	Progression	Toxicity	Other	Cumulative No.
Cycle 1	1	3	2	6
Cycle 2	3	6	0	15
Cycle 3	1	0	1	17
Cycle 4	6	1	0	24
Cycle 5	1	0	0	25
Cycle 6	1	0	0	26
Cycle 7	0	1	0	27

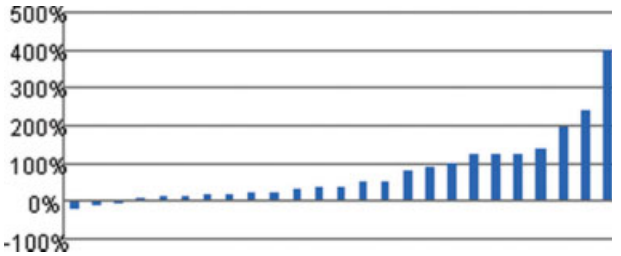

FIGURE 1. The best percentage prostate-specific antigen (PSA) change from baseline is shown. A PSA waterfall plot represents the best percentage PSA change from baseline for all evaluable patients. No PSA declines of ≥50% were observed.

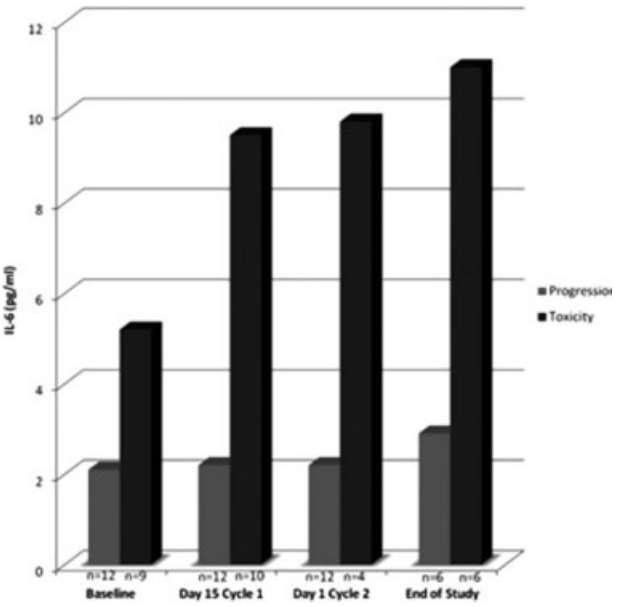

FIGURE 2. Serum interleukin-6 (IL-6) values are shown by reason for removal from treatment. Median IL-6 levels (pg/mL) were higher in patients removed from the protocol for toxicity versus progression at all time points, including baseline (5.2 vs 2.1, $P = .02$), Day 15 Cycle 1 (9.5 vs 2.2, $P = .01$), Day 1 Cycle 2 (9.8 vs 2.2, $P = .01$), and end of study (11.0 vs 2.9, $P = .09$)

Recognizing that tumor regressions are difficult to quantify objectively in patients with bone metastases, the clinical importance of delaying progression, and the available preclinical data on the antitumor effect of vorinostat, this trial was designed with a primary objective of assessing the effect of vorinostat on 6-month progression rates. Although the most optimal design would have included a control arm, the progressive nature of this disease and the availability of published historical institutional data, at the time of study design, on second-line chemotherapy in a similar population indicating that the expected 6-month progression rate is 84%[38] led us to choose a single-arm design. Although 41% of patients were taken off the study because of toxicity, thus making it difficult to assess the true efficacy of vorinostat at this dose and schedule, it is reasonable to assume that, had there been clinically meaningful antitumor activity, better results would have been expected. There was only 1 grade 4 adverse event, and grade 3 adverse events were predominantly constitutional in nature and not significantly different from dose-limiting toxicities observed in phase 1 testing.[21] However, despite dose reduction in 70% of patients in this trial, 41% of patients discontinued therapy because of toxicity. Our experience is in contrast to other reports using this agent both as monotherapy and in combination with other systemic therapies in other studies. In the phase 1 trials, once on a tolerable dose, patients could be treated for prolonged periods of time[21,22,40] with chronic adverse effects of fatigue, renal insufficiency, and weight loss reversible upon discontinuation of the drug.[21] Dose-limiting toxicities reported in phase 1 trials were not related to prior therapy or type of underlying malignancy and remained unpredictable within treatment cohorts.[21] They

were also rapidly reversible, suggesting a readily reversible metabolic process.[21]

Safety data from 86 patients with cutaneous T-cell lymphoma treated with vorinostat led to Food and Drug Administration approval of the drug, with only 9.3% of patients removed because of toxicity and 10.5% requiring dose reductions using the same dose/schedule as used in this trial, also in patients who had failed prior systemic therapies.[16] Similar results were recently reported on safety data from 476 patients who participated in the vorinostat clinical trial program, receiving vorinostat as single-agent therapy and in combination with other systemic therapies.[41]

The key question is whether our observed results are a function of the patient population studied, lack of significant antitumor activity, or both. Given the toxicity seen in this trial, leading to dose reductions in 70% of patients, it is possible that suboptimal cell inhibitory plasma concentrations of vorinostat may explain why less clinical activity was seen than expected. Without pharmacokinetics data and data from other prostate cancer settings, it is difficult to conclude whether the preclinical models were poor predictors of clinical activity or whether this agent would be more efficacious in an alternative patient population or dosing schedule. One interesting observation from this population is that patients who came off the study because of toxicity had significantly higher serum IL-6 levels at all time points (baseline, Day 15 Cycle 1, Day 1 Cycle, and end of study) as compared with patients removed from the study for progression. It is possible that, because IL-6 is associated with the inflammatory response and regulation of the systemic immune response,[39] higher levels of serum IL-6 at baseline that were not modulated by the drug predisposed patients to adverse side effects, leading to treatment discontinuation. IL-6 has been associated with nonresponsiveness to drug therapy.[29-31] However, of the 11 patients taken off the protocol because of toxicity in this study, 9 patients recovered, suggesting drug effect and not disease progression.

Toxicities were also prominent, with no significant clinical activity, in the only other reported clinical trial of histone deacetylase inhibition in prostate cancer.[42] In this phase 2 trial (n = 31) investigating romidepsin, a bicyclic depsipeptide that inhibits histone deacetylase, as front-line therapy for patients with metastatic castration-resistant prostate cancer, constitutional toxicities were common, with a 6-month disease control rate of 14% and PSA response rate of 7%. Observations from this trial and ours raise questions regarding the impact of an androgen-suppressed state as it relates to predisposing to toxicities to this class of drugs.

It is not clear why outcomes from clinical investigation of histone deacetylase inhibitors in metastatic castration-resistant prostate cancer have not matched the promising preclinical activity and scientific rationale. However, based on the current data, further investigation of vorinostat at this dose and schedule is not recommended. The lack of significant clinical activity in this trial, coupled with a comparable outcome reported with romidepsin,[42] raises concerns regarding further study of this class of drugs as single-agent therapy for treatment of castration-resistant prostate cancer, unless newer agents with a more favorable toxicity profile with substantial supportive preclinical data are introduced. Our observation of the association of IL-6 levels and removal from the study for toxicities warrants further investigation.

Conflict of Interest Disclosures

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Appendix X

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PHASE II STUDIES

Cilengitide (EMD 121974, NSC 707544) in asymptomatic metastatic castration resistant prostate cancer patients: a randomized phase II trial by the prostate cancer clinical trials consortium

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Summary *Background* Integrins are involved in prostate cancer metastasis by regulating cell adhesion, migration, invasion, motility, angiogenesis and bone metabolism. We evaluated the efficacy of two dose levels of cilengitide in patients (pts) with castrate resistant prostate cancer (CRPC). *Methods* Chemotherapy-naïve, asymptomatic metastatic CRPC pts were randomized to cilengitide 500 mg or 2,000 mg IV twice weekly using parallel 2-stage design. The primary endpoint was rate of objective clinical progression at 6-months. Secondary endpoints included clinical and PSA response rates, safety and effects of cilengitide treatment on circulating tumor cells (CTCs) and bone remodeling markers. *Results* Forty-four pts were accrued to first stage (22/arm). Median number of cycles was three in both arms (500 mg arm: 1–8; 2,000 mg arm: 1–15). At 6 months, two pts (9%) on the 500 mg arm and five pts (23%) on the 2,000 mg arm had not progressed. Best objective response was stable disease (SD) in seven pts for 9.9[8.1,20.9] months. There were three grade 3 and no grade 4 toxicities. At 12 weeks, analysis of bone markers did not reveal significant trends. At progression, bone specific alkaline phosphatase and N-telopeptide

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increased in all pts, less so in pts on the 2,000 mg arm and in pts on both arms who obtained SD at 6 months. CTCs increased over time in both arms. *Conclusion* Cilengitide was well tolerated with modest clinical effect in favor of the higher dose. The unique trial design including a shift from response rate to objective progression as the endpoint, and not acting on PSA increases was feasible.

Keywords Prostate cancer · Metastatic disease · Integrins · Angiogenesis · Cilengitide · Bone biomarkers

Introduction

Integrins are transmembrane adhesion receptors for extracellular matrix proteins that act as modulators of several key cellular functions including differentiation, survival, migration, invasion, normal and aberrant cellular growth, gene expression, and intracellular signal transduction pathways [4, 13, 21, 22, 40, 46]. The functions and expression of integrins are dysregulated in several cancer types, including prostate cancer (PCa) [19, 46].

PCa cells have a markedly different surrounding matrix than normal cells that is believed to be at least in part due to differential expression of integrins on tumor cells compared to non-tumor cells [2, 12, 19, 43, 44]. αvβ3 and αvβ5 integrins are thought to be particularly important in PCa progression playing a significant role in metastasis by regulating cell adhesion, migration, invasion, motility, and angiogenesis [5, 12, 19, 33, 35, 36, 43, 47, 48, 50]. αvβ3 integrin is also known to be critical to osteoclast migration, function and bone remodeling [17, 23, 34, 35, 38] processes known to be important in establishment and progression of bony metastases [24].

Cilengitide (Merck KGaA, Darmstadt, Germany) is a cyclic agrinine-glycine-aspartic containing peptide that binds to αvβ3 and αvβ5 with nanomolar affinity resulting in highly selective, competitive inhibitor of αvβ3 and αvβ5 integrins that in phase I studies has shown clinical activity [18, 20, 28, 32]. Responses seen in phase I trials were achieved both at low and at higher dose levels, suggesting there may be non-linear exposure/dose-response relationships, and therefore high doses or prolonged exposure are not necessarily required [18, 20, 28, 32]. The significant role of integrins in PCa metastasis identifies integrins as an important potential target molecule for treatment of this disease. We therefore conducted a phase II trial to investigate the efficacy of two dose levels of cilengitide in patients with asymptomatic castrate-resistant prostate cancer (CRPC). Correlative studies were performed to determine the effects of integrin αvβ3 and αvβ5 inhibition on circulating tumor cells and systemic bone remodeling markers.

Patients and methods

This Cancer Therapy Evaluation Program sponsored trial was conducted by the Department of Defense Prostate Cancer Clinical Trials Consortium. The protocol was reviewed and approved by the institutional review board at each participating institution and all patients provided informed consent prior to initiation of any study procedures. Eligible patients were required to have metastatic CRPC with evidence of progression by one of the following: (1.) progression of bidimensionally measurable soft tissue disease within 28 days of registration (2.) new bone lesion(s) by bone scan within 42 days of registration, and/or (3.) rising PSA with a minimum of 5 ng/ml. Patients could not have PCa related pain or visceral metastasis (lung and/or liver) and were required to have an ECOG performance status of 0–2 with adequate organ function defined by a white blood count of ≥3,000/μl, absolute neutrophil count ≥1,500/μl, platelet count ≥100,000/μl, creatinine ≤1.5 × upper limits of normal, bilirubin within normal limits, AST and ALT ≤2.5 × upper limits of normal. Luteinizing hormone-releasing hormone agonists were continued. Discontinuation of all nonsteroidal antiandrogens (28 days for flutamide and 42 days for bicalutamide) was required. Prior chemotherapy was not permitted. Patients could have had one prior biologic therapy (non-cytotoxic). Patients on stable doses of bisphosphonates which had been started no less than 6 weeks prior to protocol therapy, who showed subsequent tumor progression, were permitted to continue on this medication, however, initiation of bisphosphonate therapy immediately prior or during study was not permitted. No concomitant therapy (other than LHRH agonists) to treat PCa was permitted. Men of reproductive potential had to agree to use effective contraception. Patients with a "currently active" second malignancy other than non-melanoma skin cancers were not eligible. Patients were not considered to have a "currently active" malignancy if they had completed therapy and were without evidence of disease for 2 years.

Treatment plan

Patients were randomized 1:1 to either 500 mg or 2,000 mg with stratification for bisphosphonate usage. Cilengitide was administered as a 1 h intravenous infusion twice weekly per 6 week cycles. Toxicity was assessed using NCI-common terminology criteria version 3.0 and dose reductions were specified for grade 3 or 4 toxicities. For the 500 mg arm, dose -1 was 400 mg and dose -2 was 300 mg. For the 2,000 mg arm, dose -1 was 1,600 mg and dose -2 was 1,200 mg. There were no planned breaks between cycles. If clinically indicated, interruption of treatment was

allowed for a maximum of 2 weeks at a time with a maximum of two treatment interruptions.

Duration of therapy, monitoring and response assessment

In the absence of toxicity or symptomatic progression, patients were to receive a minimum of 2 cycles (12 weeks). Patients were monitored by history and physical exam, toxicity assessment, and PSA every 3 weeks. Response assessment by bone scan and CT scan and/or other appropriate imaging was performed every 12 weeks. Patients with symptomatic progression were removed. Patients with evidence of asymptomatic progression by CT or bone scan at first assessment (12 weeks) were to receive an additional cycle of treatment followed by repeat imaging 6 weeks (1 cycle) later. Patients with further progression were removed from protocol with time of progression recorded as first progression. Patients with stable disease or better continued therapy till further progression. PSA progression alone was not considered progression per protocol. All patients were followed until progression.

End points definition

Time to progression was defined as the time from the first day of treatment until the date progressive disease or death was first reported. Progression was defined by any one or more of the following parameters: 1.) Measurable disease progression by RECIST criteria. 2.) Progression by bone scan (development of ≥2 new lesions). 3.) Pain progression (pain due to prostate cancer requiring intravenous, intramuscular or subcutaneous opioid therapy administered as a single dose; oral or transdermal opioid analgesic use administered for 10 out of 14 consecutive days, and/or requiring radionuclide or radiation therapy).

Measurable disease responses were defined using RECIST criteria. Bone disease response was evaluated by bone scan with disease characterized as stable or improved if no new lesions and no new pain in an area that uptake was previously visualized versus progression as defined by the appearance of two or more new skeletal lesions. PSA response was defined based on the PSA Working Group Consensus Criteria [7].

Endpoints and statistical design

The primary objective of this trial was to evaluate efficacy, as measured by the rates of objective clinical progression at 6-months (not including PSA), associated with the two dose levels of cilengitide. The assumptions for this trial were based on the progression rates of the control arm of the randomized phase III trial testing atrasentan in a similar patient population. At the 3-month time point, the historical untreated controls with metastatic CRPC had a 50% progression rate by bone scan [10] therefore we projected this group to have a 75% progression rate at 6-months. It was hypothesized that cilengitide would lower this progression rate to 55% at 6-months. A modified version of the randomized selection design [45] was utilized to compare two dose levels of cilengitide, 500 mg and 2,000 mg. The plan was for 53 patients to be randomized to each dose level using a two-stage design in a stratified manner to ensure equal percentages of prior bisphosphonate use. For each dose level, an independent evaluation was planned. If six or more of the first 20 patients were found to be progression-free at 6-months, second stage would open for that dose level and an additional 33 patients would be accrued. If 17 or fewer of the 53 patients were progression-free at 6-months, at the second stage, the dose would be considered uninteresting for further study.

Upon study completion, the planned decision rule for selecting a dose level for further study is as follows: (1) if neither arm shows activity, no arm is selected, (2) if only one arm shows activity, that arm is selected, (3) if both arms show activity and the difference in 6-month progression rates is greater than 5%, then the arm with the highest rate is selected, (4) if both arms show activity but the difference in progression rates is less than 5%, the selection will be based on a combination of internal and external data. This study was designed to accrue 106 total subjects, 53 per arm to allow selection of the superior dose level with 90% probability.

Secondary endpoints included objective and PSA responses, time to clinical and PSA progression, toxicities, and biological correlates. The objective response rates and 95% confidence interval is reported. Time to clinical and PSA progression were estimated using product limit estimates of the Kaplan-Meier method. Biological correlate comparisons were tested within strata by dose level using the Wilcoxon rank test.

Correlative biology studies

The objective of correlative studies performed was to determine the effects of integrin $\alpha v\beta 3$ and $\alpha v\beta 5$ inhibition on total circulating tumor cells (CTCs) and endothelial cells (CECs) isolated from peripheral blood and on systemic bone remodeling markers.

Peripheral blood samples were analyzed for CTCs using the CellSearch® reagents (Immunicon Corporation, Huntington Valley, PA) [30] and for CECs using the CellTracks® reagents (Immunicon Corporation) [39]. Evaluation of CTC and CEC was performed by Immunicon. Bone-specific alkaline phosphatase (BAP), an indicator of bone production was measured using a commercially available ELISA, Metra®

BAP (Metra Biosystems: Quidel Corporation, Mountain View, CA), and serum N-telopeptide (NTx), a specific biochemical indicator of bone resorption using Osteomark NTX® (Wampole Laboratories, Princeton, NJ). Intact osteocalcin (OCN), an indicator of bone production was measured by competitive EIA (NovoCalcin, Metra Biosystems: Quidel Corporation, Mountain View, CA).

Results

Between 1/17/05 and 1/24/07, 44 patients were registered to protocol (22 pts/arm) at five centers. Table 1 describes baseline patient characteristics by dose level. The median age was 72 (range: 52–85). 72% of patients had a performance status of 0. Patients were well balanced between arms with the exception of a statistically significant difference with younger age (median 67 vs. 73 years), lower baseline PSA, (median 26 vs. 65 ng/ml) and less bone progression at time of registration on the 2,000 mg arm. All patients are off protocol therapy with a median number of cycles of 3 (range 1–8 on the 500 mg arm and 1–15 on the 2,000 mg arm).

Adverse events

Therapy was very well tolerated with no grade 4 or greater adverse events (AEs) and only three grade 3 AEs (neutropenia, and transient lymph node pain and enlargement in one patient). Table 2 describes in detail AEs by type and grade by dose level. Only one patient required dose reduction to -1 dose level.

Table 1 Baseline patient characteristics

	500mg (n=22)	2,000mg (n=22)
Age		
Median	73 (59–84)	67 (52–85)
Race		
White	18	20
African American	2	2
Asian	2	0
Performance status		
0	16	15
1	6	6
Unknown	0	1
Zoledronic acid usage[a]	6 (27%)	5 (23%)
PSA (ng/ml)		
Median	65 (6–870)	26 (5–621)
Disease progression at registration		
PSA	21 (95%)	19 (86%)
Soft tissue	5 (23%)	11 (50%)
Bone	13 (59%)	3 (14%)

[a] Zoledronic acid was permitted if started ≥6 weeks prior to registration

Table 2 Treatment related adverse events

Adverse event	Grade	500mg	2,000mg
Lymph node pain	3	1	0
Lymphatics-other	3	1	0
↓ Neutrophil count	3	0	1
Anorexia	2	2	0
Arthritis	2	0	1
Bone pain	2	1	0
Constipation	2	1	1
Dehydration	2	1	0
Fatigue	2	4	3
Glucose tolerance impaired	2	1	0
Headache	2	0	1
↓ Hemoglobin	2	0	2
Hyperglycemia	2	0	1
Hypoalbuminemia	2	0	1
Hypotension	2	1	0
Leukopenia	2	1	0
Musculoskeletal disorder	2	0	1
Nausea	2	1	0
↓ Neutrophil count	2	1	1
Pain in extremity	2	1	0
Tooth infection	2	0	1

Includes all grade 2 and above toxicities considered possible, likely, or probably related to cilengitide

Efficacy results

At the time of interim analysis after first stage of accrual, 91% (95% CI (71–99%) of patients on the 500 mg arm had progressed at the 6 month assessment (2/22 pts not progressing) and 77% (55–92%) on the 2,000 mg dose arm (5/22 pts not progressing) (Fig. 1)

Best response obtained was stable disease (SD). Overall there were 15 pts with SD as their best response at any time during the trial (median 6.9 months, range [2.8,20.9]), however per protocol specified requirement of SD at 6 months, 7 fulfilled the criteria (median 9.9 months, range [8.1,20.9]. There was no significant difference in median duration of SD between arms (p=0.95) (2,000 mg (n=9) duration SD=8.1 months; 500 mg arm (n=6) duration SD=6.9 months) although the study was not designed to compare arms. Twenty-seven patients had asymptomatic progression at first assessment (12 weeks). Of these 27 patients, 13 (48%) elected to continue treatment per protocol. 31% of these 13 patients achieved a best response of SD, 69% experienced confirmed progression.

These patients remained on treatment for a median of one additional cycle (range 1–3).

There was one PSA response on the 2,000 mg arm and none on the 500 mg arm. At first assessment, 4/44 (9%) of patients had a stable PSA. Median time to PSA progression was 0.7 months (95% CI 0.7, 1.4) on the 500 mg arm and 2.3 months (95% CI 1.3, 4.2) on the 2,000 mg arm (p= 0.0001). There was no significant correlation between baseline PSA or baseline bone markers and study-defined objective or PSA progression.

All patients are off study; five (11%) withdrew consent, 34 (77%) secondary to progression [19 (56%) in bone, 14 (44%) in soft tissue] and 5 (11%) for other reasons. In an exploratory analysis of the 34 patients who had progression by objective and PSA criteria, study defined objective progression occurred at a median of 1.9 months (range: −1.5–9.2 months) after PSA progression.

Correlative studies

There were no significant differences between arms at baseline in serum bone markers BAP, NTX, and OCN with the exception that OCN was higher in the 500 mg arm in patients not receiving zoledronic acid (Table 3). OCN was most likely higher in patients not receiving zoledronic acid due to increased bone turnover in these patients. There were no significant biologic trends at first assessment (12 weeks). At time of progression, BAP and NTX increased in all patients, however less so in patients on the 2,000 mg arm and in patients on both arms who obtained SD at 6 months.

Samples for assessment of CTCs and CECs were available for all patients at baseline. At week 12, samples were available for 32 pts for CTC and 28 pts for CEC assessment. Histograms did not differ by dose level (Fig. 2). Time to progression (TTP) was not different between patients with 0–5 CTCs at baseline compared to those with >5 CTCs at baseline. TTP was slightly better for the group with 0–5 CTCs at cycle 2 compared to those with >5 CTCs. This was not statistically significant. The group of patients with a decrease in CTCs at cycle 2 compared to baseline had a slight advantage in TTP compared to those whose CTCs increased between baseline and cycle 2. This was not statistically significant. There was no correlation between CEC number and progression.

Discussion

We evaluated two dose levels of cilengitide, an inhibitor of αvβ3 and αvβ5 integrins, in chemotherapy naïve patients with asymptomatic, metastatic CRPC using a 6 month non-progression endpoint. The choice of this endpoint repre-

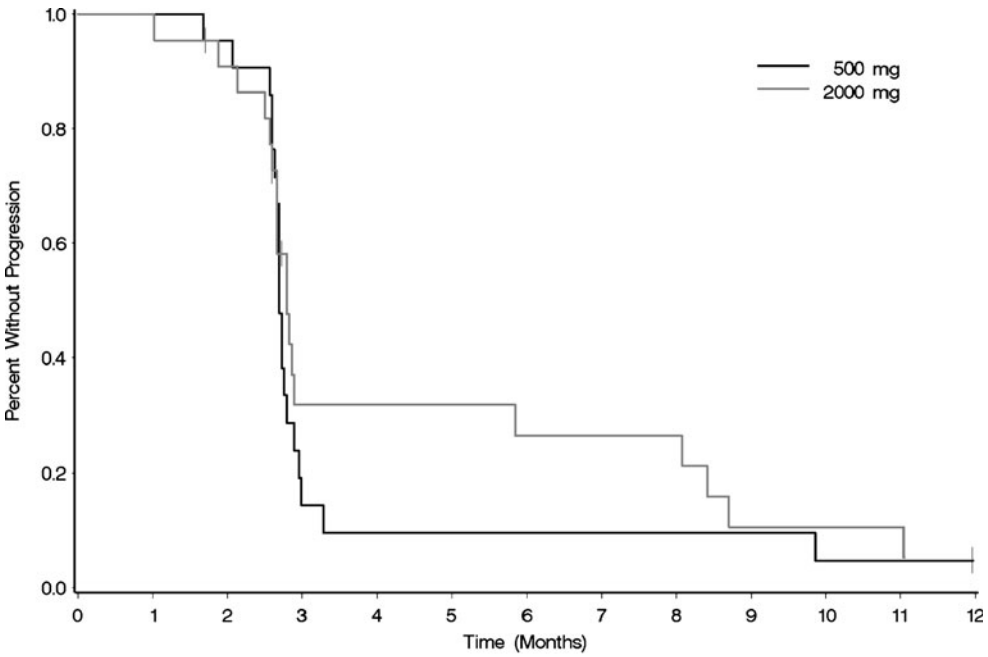

Fig. 1 Time to objective progression

Table 3 Baseline serum bone turnover markers by arm

		Median	Min	Max	*p*-value
No zoledronic acid					
BAP (U/L)					0.97
	500 mg	3.41	1.76	256.13	
	2,000 mg	3.70	1.69	40.05	
NTX (nM BCE)					0.54
	500 mg	16.53	8.79	48.41	
	2,000 mg	15.42	8.43	46.52	
Osteocalcin (ng/ml)					0.01
	500 mg	11.28	7.98	17.28	
	2,000 mg	8.45	2.91	14.04	
Zoledronic acid					
BAP (U/L)					0.99
	500 mg	2.51	1.74	3.74	
	2,000 mg	2.34	1.90	23.78	
NTX (nM BCE)					0.34
	500 mg	12.53	8.71	18.71	
	2,000 mg	10.76	4.97	27.73	
Osteocalcin (ng/ml)					0.34
	500 mg	8.61	7.29	10.67	
	2,000 mg	6.76	1.70	12.51	

BAP bone specific alkaline phosphatase, *NTX* N-telopeptide, *OCN* intact osteocalcin, nanomolar bone collagen equivalents, *U/L* units/liter, *ng/ml* nanograms/milliliter

sents a shift in paradigm from using PSA decline rates or response rates to a clinically meaningful endpoint. The rational was further supported by the hypothesized cytostatic mechanism of action. Recognizing the difficulties in interpreting early changes, this trial pioneered a trial design that allowed patients with evidence of asymptomatic progression at first assessment to continue on study with an interim follow up scan to confirm progression. Both approaches proved feasible.

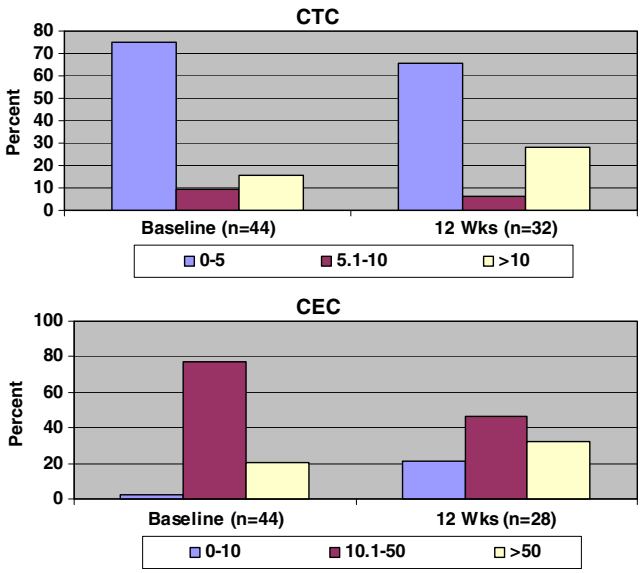

Fig. 2 Histogram of circulating tumor cells/circulating endothelial cells

Since neither arm, at the time of prespecified interim analysis (after first stage of accrual), met the prespecified cutoff of 6 (27%) or more patients progression free at the 6 month evaluation, the study did not proceed to second stage. Although neither arm reached the prespecified activity level, clinical (a trend towards less progression at the 6 month assessment; 91% and 77% on the 500 mg arm and the 2,000 mg dose arm, respectively) and correlative studies results suggest that the 2,000 mg dose level has more but modest activity over the 500 mg dose.

Markers of bone turnover are indicative of bone resorption and formation reflecting osteoclastic and osteoblastic activity, respectively and are proving to be a useful tool for measuring the efficacy of bone targeted therapy [8, 9, 26, 49]. Increased N-telopeptide and bone specific alkaline phosphatase have been associated with adverse clinical outcomes, including shorter time to skeletal events, disease progression and death [6, 11, 27, 41]. In this trial, bone turnover markers of patients treated on the 2,000 mg arm tended not to increase as much at time of progression although was not statistically significant. Additionally, patients on both arms that obtained stable disease at 6 months showed a similar trend suggesting an effect of cilengitide on the bone microenvironment in some patients. Another promising biomarker in CRPC investigated in this study is CTCs. Recent studies of CTCs in CRPC have evaluated the ability of CTCs to be used as a surrogate for

overall survival [14, 16, 29, 30]. Less than 5 CTCs/7.5 mL at baseline and post-treatment has correlated with improved overall survival. In this study, there was a trend towards increased time to progression in patients on the 2,000 mg dose arm with less than or equal to five CTCs at first assessment. In all patients, there was a non-significant trend towards increased time to progression in patients with 0–5 CTCs at cycle 2 compared to those with >5 CTCs at cycle 2, again suggestive of possible activity in some patients though the numbers are too small for any major conclusion.

It is possible that significant clinical activity was not demonstrated despite a signal of biologic activity because of incomplete integrin inhibition which could have been impacted by dose or schedule. In phase I testing, no clear pattern of cilengitide toxicity could be determined and no maximum tolerated dose was reached [18, 28, 32] with responses achieved at both low and high dose levels [1, 18, 20, 28, 32]. However, disease specific phase II testing points towards a modest increased efficacy at higher dose levels [32, 37] which is supported in our current trial. In a phase IIa study investigating 500 mg and 2,000 mg dosing in patients with recurrent glioblastoma [37], pharmacokinetic studies revealed significantly greater exposures among the 2,000 mg cohort. However, in prostate cancer, which is not known to be as vascular as brain tumors, it is possible that even the 2,000 mg dose may not have been sufficient to effectively block integrin receptors to result in a biologic effect due to the short plasma half-life of cilengitide of 2.5–4 h [28, 32]. Therefore dosing chosen for this trial may not have been optimal with the potential need for continuous infusion or more frequent administration to observe a significant biologic effect. It is also possible that alternative integrins not blocked by cilengitide may have a more significant role in prostate cancer. To date, the specific functions of integrins, their ligands, and their modulators in prostate cancer progression are incompletely understood [3, 15, 19, 25, 31, 33, 43]. This study suggests that inhibition of integrins may have some biologic effect but perhaps alternative or more inhibition is necessary. Because tumors can overcome integrin requirements through upregulation of integrin-initiated intracellular signaling pathways, inhibition of integrin-dependent signaling components, including FAK, Src, and P13K may serve as complimentary chemotherapeutic targets [46].

Because of the lessons learned investigating other bone targeted therapies suggesting patients may have been taken off therapy prematurely, we pioneered this study design to avoid premature withdrawal of the agent. Patients were permitted to continue on trial until confirmed progression. Twenty-five patients had asymptomatic progression at first assessment (12 weeks). Of these 24 patients, 13 (54%) elected to continue treatment. Thirty-one percent of these 13 patients achieved a best response of SD. 69% experienced confirmed progression at the second assessment after cycle 3 (18 weeks). This is one of the first trials to test the feasibility of this concept. Since this trial was designed in 2004, the Prostate Cancer Clinical Trials Working Group has published consensus recommendations for clinical trial conduct including this concept [42].

Conclusions

In summary, cilengitide was well tolerated, however, did not meet the protocol prespecified decrease in the 6 month progression rate at either dose level. The clinical and biomarker results suggest a potential improved, though, modest effect with the 2,000 mg dose. The findings from this study therefore support further investigation of integrin inhibition with more active agents in this disease.

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Appendix Y

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PHASE II STUDIES

Oral enzastaurin in prostate cancer: A two-cohort phase II trial in patients with PSA progression in the non-metastatic castrate state and following docetaxel-based chemotherapy for castrate metastatic disease

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Summary *Purpose*: Enzastaurin is an oral serine/threonine kinase inhibitor of the beta isoform of protein kinase C that may have therapeutic activity in prostate cancer. We explored the efficacy of enzastaurin on two cohorts of patients with prostate cancer progression in the castrate state. *Patients and Methods*: A two-cohort phase II trial was conducted, with both groups participating simultaneously. Cohort 1 consisted of patients with non-metastatic castrate prostate-specific antigen progressive disease. Cohort 2 consisted of patients with castrate metastatic disease with progression following docetaxel-based chemotherapy. Patients in both cohorts received 500 mg/day enzastaurin. *Results*: Therapy was well tolerated in both cohorts. One complete response was observed in Cohort 1, with limited activity in the majority of patients. In Cohort 2, no objective responses were seen and the median progression-free survival (11 weeks [90% confidence interval: 7.6, 11.7]) did not differ from the historical control. *Conclusions*: Enzastaurin as a single agent has limited activity in castrate progressive prostate cancer. Evaluation in combination with docetaxel is ongoing.

Keywords Prostate cancer · Enzastaurin · Prostate-specific antigen · Clinical trial

Trial registry: ClinicalTrials.gov.
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Introduction

Prostate cancer is the second-leading cause of cancer-related death in men in the United States [1]. This underscores the need for research to improve treatment outcomes in prostate cancer. While the majority of men with newly diagnosed prostate cancer undergo curative intent local therapy (surgery or radiotherapy), 20–40% of men will manifest evidence of disease persistence or recurrence, typically as prostate-specific antigen (PSA) recurrence [2, 3]. Although salvage options including radiotherapy, cryotherapy, and surgery may impact a subset of patients, many patients ultimately receive androgen deprivation therapy either in the setting of PSA-only disease or when manifesting clinically evident metastatic disease [4]. Management options for disease progression,

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despite castrate testosterone levels in the setting of metastatic disease, may include second-line hormonal therapy with agents such as steroids or ketoconazole, or docetaxel-based chemotherapy [5, 6].

After many decades of limited progress, the past several years have seen important developments in the basic understanding of prostate cancer biology [7]. Novel insights into androgen receptor biology have led to the development of a new generation of androgen receptor targeted therapeutics and have confirmed the widely used terms "androgen-independent" and "hormone-refractory" to be misnomers [8]. Despite recent progress, disease progression following docetaxel-based chemotherapy remains ubiquitous and there are limited therapeutic options. New effective therapies are urgently needed.

Enzastaurin is an oral serine/threonine kinase inhibitor of the beta isoform of protein kinase C (PKCβ), one of a family of enzymes integral to numerous functions in normal and cancer cells including cell growth, proliferation, and programmed cell death [9–11]. Enzastaurin and its metabolites also inhibit other intracellular signaling proteins that are important to tumor growth and tumor cell-induced angiogenesis, such as phosphatidylinositol-dependent kinase 1 (PDK1), glycogen synthase kinase 3 beta (GSK-3β), p70S6 kinase, and phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway [12].

Given the known effect of enzastaurin on key signaling pathways that regulate cell growth, the question becomes whether enzastaurin impacts those pathways in prostate cancer. High expression levels of various PKC isozymes, including PKCβ, have been found in prostate cancer relative to benign hyperplasia [13]. Additionally, Graff and colleagues demonstrated the ability of enzastaurin to suppress proliferation in the low micromolar range in a prostate cancer derived cell line (PC-3) [12]. This preclinical evidence, along with the favorable clinical safety profile of enzastaurin and its promising activity in various cancers, led to the decision to test enzastaurin in patients with prostate cancer [14, 15].

We opted to explore the single-agent activity in both castrate PSA-only disease and castrate metastatic disease with progression following docetaxel-based chemotherapy. As this was a proof-of-concept study, a phase II design was chosen, with historical progression-free survival (PFS) data from a phase III trial placebo group [16, 17] used as a comparator for the metastatic cohort. The primary efficacy variable of the PSA-only cohort was objective response, as assessed by a decline of at least 50% of the serum level of PSA. As the IC_{90} of enzastaurin for PKCβ is 70 nM (*in vitro* kinase assays) (data on file) and approximately 95% of the drug is protein-bound in human plasma, 1400 nM was chosen as a targeted mean steady-state plasma concentration for clinical activity [15]. A 500 mg/day enzastaurin yields this targeted plasma concentration and is well tolerated and active; thus, this was chosen as the dose for this study. To facilitate attaining near steady-state concentrations of enzastaurin in a relatively short period of time (<7 days), the study design included a Day 1 loading dose of 1,125 mg.

Using a panel of efficacy and safety measures, this study aimed to identify whether enzastaurin had demonstrable clinical activity as monotherapy in patients with asymptomatic, castrate, PSA-progressive, or docetaxel-resistant metastatic disease. Additional measures sought to characterize the tolerability and pharmacokinetics of the enzastaurin regimen in this patient population.

Methods

Patients

This study investigated two patient cohorts. Patients in Cohort 1 were required to have castrate, PSA-progressive disease (rising PSA values of ≥5 ng/mL) without clinical or radiographic evidence of metastatic disease, and with testosterone levels of <50 ng/dL following standard anti-androgen withdrawal. Patients could not have received any prior systemic chemotherapy for prostate cancer and no prior chemotherapy for any other indication within 2 years of study entry. Patients in Cohort 2 were required to have either docetaxel-resistant castrate metastatic prostate cancer, defined as disease progression while receiving docetaxel, or evidence of disease progression following docetaxel, defined as a 25% increase in PSA from the post docetaxel value, radiographic progression in known metastatic sites, or development of new sites on bone scan or computed tomography (CT) imaging. Patients who discontinued a docetaxel-containing regimen due to toxicity or any other reason not related to disease progression while on treatment, and who were not able to complete at least 2 cycles, were not eligible. Patients who received >1 cytotoxic regimen for advanced prostate cancer were also ineligible. Eligible patients in both cohorts were ≥18 years of age, and had Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and adequate organ function.

Patients in both cohorts were excluded if they received concurrent administration of systemic anticancer therapy (except luteinizing hormone-releasing hormone agonist), received concurrent administration or were unable to discontinue enzyme-inducing antiepileptic drugs, had a serious concomitant disorder, had a serious cardiac condition within 6 months, received treatment with an experimental drug within 30 days prior to enrollment, or were unable to swallow tablets.

All patients gave written informed consent, including consent to the collection of blood samples, as specified by the protocol.

Study design and treatment

The primary objective for Cohort 1 was to determine the PSA response rate following 500 mg/day oral enzastaurin. The primary objective for Cohort 2 was to determine PFS after an identical regimen. Secondary objectives for both cohorts included evaluating the safety and tolerability of enzastaurin and assessing the PFS rate for Cohort 1 and the response rate in Cohort 2. Details of the definitions of efficacy measures for each cohort are found in Table 1.

This multicenter, open-label, single-arm, two-cohort, nonrandomized, phase II study aimed to enroll 86 patients (43 per cohort). Patients received 500 mg enzastaurin once daily within 30 min of completing a meal, with a loading dose of 1,125 mg enzastaurin (375 mg, three times daily) on Day 1 of Cycle 1 (28 day cycles). Patients continued with standard androgen deprivation therapy in addition to enzastaurin. Patients continued on study for up to 3 years, or until developing disease progression or unacceptable adverse events, including treatment omission for >4 weeks due to toxicity (>2 weeks in the case of grade 3/4 nausea or vomiting) or failure of a toxicity to resolve to ≤ grade 1 within 4 weeks following dose reduction. Enzastaurin administration was omitted for: absolute neutrophil counts (ANC) $<0.5\times10^9$/L lasting longer than 7 days, ANC $<1.0\times10^9$/L with fever or platelet count $<25\times10^9$/L, grade 3/4 transaminase elevation, or other grade 3/4 nonhematologic toxicity considered clinically relevant. If the event resolved to ≤ grade 1 or baseline value, the patient began therapy again at 250 mg/day, with re-escalation to the full dose at the discretion of the investigator if the event did not occur after 28 days of therapy.

Cohort 1 employed Simon's two-stage optimum design, requiring 43 patients [18]. Eighteen patients were to be enrolled for the first stage, and a further 25 for the second stage. If 2 or fewer patients from the first stage had an objective response, enrollment into the second stage was to cease and the cohort was to be closed. Otherwise, Cohort 1

Table 1 Definition of efficacy measures for Cohorts 1 and 2

Cohort 1	Cohort 2
Objective Response = response based on a decline in serum PSA level as delineated:	Objective Response = response based on these composite criteria:
PSA Complete Response = decrease in PSA to an undetectable level (<0.2 ng/mL), confirmed by a second value 4 weeks later, with no clinical or radiographic evidence of disease.	For patients with measurable disease per RECIST[a]:
PSA Partial Response = decrease in PSA of ≥50% from a baseline value of >5 ng/mL, confirmed by a second value 4 weeks later, without clinical or radiographic evidence of disease.	Complete Response = complete response per RECIST, plus undetectable PSA confirmed by a second value 4 weeks later and normalization of bone scan.
Progression = first occurrence of either:	Partial Response = partial response per RECIST, plus ≥50% decline from baseline in absolute value of PSA, with confirmation 4 weeks later, and stable or improved bone scan.
(1) PSA Progression: defined for patients in whom a 50% decline in PSA had not been achieved as a 25% increase over baseline or nadir PSA level (whichever was lower) AND an increase in the absolute value of PSA level by 5 ng/mL, confirmed by another value of PSA ≥4 weeks later, and defined for patients in whom a 50% decline in PSA had been achieved as a 50% increase over the nadir AND an increase in the absolute value of PSA level by 5 ng/mL that was confirmed by another PSA level ≥4 weeks later; or	Progression = the occurrence of any of these events: the appearance of 2 or more new lesions on bone scan, confirmed 6 weeks later; a skeletal event such as any pathological bone fracture or need for palliative radiotherapy; symptomatic progression such as worsening of ECOG performance status, weight loss >10% from baseline, or increase in analgesic consumption and pain; death due to any cause.
(2) Objective Progression: development of radiographic evidence of metastatic disease irrespective of PSA value, or	For patients with bone disease only:
(3) Death due to any cause.	Complete Response = normalization of bone scan with undetectable PSA confirmed by a second value 4 weeks later
	Stable Disease = any patient who cannot be classified as having a complete response or disease progression
	Progression = as defined above

ECOG Eastern Cooperative Oncology Group; *PSA* prostate-specific antigen; *RECIST* response evaluation criteria in solid tumors

[a] RECIST criteria for measuring tumor response: CR = disappearance of all target lesions; PR = 30% decrease in the sum of the longest diameter of target lesions; PD = 20% increase in the sum of the longest diameter of target lesions; SD = small changes that do not meet above criteria

would continue enrolling until there were 43 evaluable patients. Final analysis of the primary endpoint of Cohort 1 was to occur prior to study closure, at the point when all patients had been enrolled for ≥9 months or had discontinued or completed the study. Study closure for this cohort occurred either when ≥70% of patients had progressed, died, completed, or discontinued from the study, or when all patients had been on study >2 years. Only the primary analysis and a reduced set of secondary analyses were to be conducted if the study did not continue in the second stage.

Cohort 2 study closure and analysis of the primary endpoint occurred either when ≥39 out of 43 enrolled patients had progressed, died, completed, or discontinued from the study, or when all patients had been on study >2 years.

Baseline and treatment assessments

Before entering the study, patients underwent a medical history and physical examination, tumor assessment by CT and bone scan, hematology profile, and blood chemistry tests. Additionally, samples were collected for serum PSA and testosterone. Assessments were continued at each cycle except for the imaging studies, which were performed every 3 cycles of treatment (12 weeks) and 4–6 weeks after the first evidence of response. Samples for pharmacokinetics were collected at baseline and pre-defined regular intervals. Samples for translational research (whole blood, plasma, serum) were also collected; however, analyses were not performed due to a shortage of samples and a lack of objective tumor/PSA responders. Patients were assessed for toxicity before each cycle according to the Common Terminology Criteria for Adverse Events, Version 3.0.

Pharmacokinetics

Plasma samples for pharmacokinetic evaluation were assayed for enzastaurin and its metabolite LSN326020 (Advion BioServices, Inc., Ithaca, NY) using validated methodology. Blood was collected from each patient at Cycle 1, Day 1 (1 to 4 h after the first dose of the loading dose) and Cycle 2, Day 1 (pre-dose, and 1 to 4 and 5 to 10 h post-dose). Plasma concentration versus time data, together with information on dosing and patient characteristics, were pooled and analyzed using a population pharmacokinetic analysis approach [19]. Nonlinear mixed effect modeling (NONMEM VI) was used for the post-hoc estimation of the pharmacokinetic parameters of enzastaurin and its metabolite. The base model employed a two-compartment structural model with first order absorption and elimination, parameterized in terms of absorption rate, oral clearance, distributional clearances, and central and peripheral volumes for parent and metabolite.

Statistical plan

Efficacy and safety results of this study are presented within each cohort by grouping all centers. The Cohort 1 population for efficacy analyses consisted of enrolled patients who had received ≥1 dose of enzastaurin and who had a valid baseline PSA assessment and ≥1 valid post-baseline PSA assessment. The Cohort 1 population for safety analyses and the Cohort 2 population for efficacy and safety analyses consisted of enrolled patients who received ≥1 dose of enzastaurin.

The Simon's two-stage optimum design [18] used for Cohort 1 had a Type I error (alpha)=0.05 for testing a null hypothesis of an objective response rate of 10% or less, and a Type II error (beta)=0.20 (80% power) for an alternative hypothesis of a PSA response rate of 25%.

The primary efficacy analysis of Cohort 2 compared the median PFS in this cohort with the median PFS observed for placebo in the Phase 3 Satraplatin and Prednisone against Refractory Cancer (SPARC) trial, which was conducted in the second-line setting and used a similarly defined PFS as the primary endpoint [16, 17]. A one-sided 0.05 level test had approximately 80% power to detect a median PFS of 14.2 weeks, compared with a historical control median PFS of 9.7 weeks (from the SPARC trial). This was calculated using the Lawless formula as implemented by the Southwest Oncology Group [20].

In each cohort, all efficacy and safety analyses were conducted on enrolled patients who received ≥1 dose of enzastaurin. Descriptive statistics varied according to type of outcome. For ordinal or continuous variables, descriptive results included mean, observed sample size, standard deviation, minimum, median, and maximum. Confidence bounds for the mean were two-sided 90% confidence intervals (CIs) calculated using the standard formulation based on Student's *t*-distribution. Discrete outcomes (including objective response rate) were presented as category frequencies and percentages, noting the numerator and denominator used to derive the percentage. Two-sided 90% CIs for these category percentages were calculated using an exact method based on the method of Collett [21]. All analyses used Statistical Analysis Software (SAS) Version 8 or higher. Kaplan Meier methods [22] were used for time to event endpoints.

Results

Patients, treatment, and pharmacokinetics

Cohort 1 This cohort was terminated early for futility because only one responder was observed in the interim

analysis of the first 18 enrolled patients. During the period the interim data were being analyzed, 13 additional patients were enrolled, for a total enrollment of 31 patients at nine centers in the United States between February 2007 and May 2009. Patient characteristics are listed in Table 2. Most patients were Caucasian with good performance status (ECOG 0-1). The mean on-study PSA was 28.1 ng/mL. All 31 patients were evaluable for toxicity and 27 patients were evaluable for response (four patients did not have a valid on-study or post-therapy PSA). One patient originally enrolled in Cohort 2 but was inadvertently coded as a Cohort 1 patient. This patient's response and toxicity data have been analyzed within Cohort 1 as per intent-to-treat analysis, and represent the one patient in this cohort who died of disease progression. Patients were on study drug for an average of 136 days (range, 56–447 days), and received a mean of 5.1 cycles, with an actual mean dose of 506 mg/day (standard deviation [SD] = 80.5 mg/day). Analysis of data from 20 patients yielded a mean enzastaurin average concentration under steady state conditions during multiple dosing ($C_{av,ss}$) of 941 nmol/L and a mean enzastaurin metabolite $C_{av,ss}$ of 901 nmol/L.

Table 2 Patient characteristics at baseline: Cohort 1

	Cohort 1 (*N*=31)
Age, years	
Median	72
Range	52–88
Ethnicity, *n* (%)	
Caucasian	27 (87)
African American	3 (10)
Hispanic	1 (3)
Mean Gleason score[a]	7.5
ECOG performance status , *n* (%)	
0	22 (71)
1	9 (29)
Mean PSA level (ng/mL)	28.1
Mean testosterone level (nmol/L)	0.8[b]
No. prior systemic hormonal therapy regimens, *n* (%)	
0	1 (3)
1–3	22 (71)
>3	8 (26)

ECOG Eastern Cooperative Oncology Group; *No*. number; *PSA* prostate-specific antigen

[a] Data available for 26 patients. The Gleason score is used to numerically characterize the degree of differentiation and normal prostate architecture in pathology specimens, with 2 as the lowest possible score and best prognosis, and 10 as the highest possible score, with poorest prognosis

[b] 0.8 nmol/L=23 ng/dL

Cohort 2 Between January 2007 and January 2008, 42 patients were enrolled at nine centers in the United States. Patient characteristics are listed in Table 3. Most patients were Caucasian with good performance status (ECOG 0-1). Two patients were ineligible due to prior treatment with non-docetaxel based chemotherapy; however, these patients have been included in the analysis for both toxicity and efficacy. Patients were on study drug for an average of 69 days (range, 6–220 days) and received a mean of 3.2 cycles, with an actual mean dose of 523.6 mg/day (SD= 129.6 mg/day). Analysis of data collected from 36 patients yielded a mean enzastaurin $C_{av,ss}$ of 1,080 nmol/L and a mean enzastaurin metabolite $C_{av,ss}$ of 958 nmol/L.

Safety

Cohort 1 All 31 patients were evaluable for toxicity. Therapy was well tolerated, with most common treatment-related toxicities being grade 1 or 2 (Table 4). There were no therapy-related study discontinuations or deaths. There were no dose omissions due to toxicity; however, 1 patient required a dose reduction due to grade 3 hyponatremia.

Cohort 2 All 42 patients were evaluable for toxicity. There were no therapy-related deaths; however, 2 patients died within 30 days of study treatment discontinuation due to disease progression. Thirteen (31%) patients received dose

Table 3 Patient characteristics at baseline: Cohort 2

	Cohort 2 (*N*=42)
Age, years	
Median	72
Range	50–81
Ethnicity, *n* (%)	
Caucasian	39 (93)
Asian	2 (5)
Hispanic	1 (2)
Mean Gleason score[a]	7.6
ECOG performance status, *n* (%)	
0	14 (33)
1	26 (62)
2	2 (5)
Mean PSA level (ng/mL)[a]	341

ECOG Eastern Cooperative Oncology Group; *PSA* prostate-specific antigen

[a] Data available for 40 patients. The Gleason score is used to numerically characterize the degree of differentiation and normal prostate architecture in pathology specimens, with 2 as the lowest possible score and best prognosis, and 10 as the highest possible score, with poorest prognosis

Table 4 Summary of key CTCAE drug-related toxicities (worst grade) for patients in Cohort 1 and 2

	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)
Cohort 1 (N=31)[a]			
Fatigue	8 (26)	2 (7)	1 (3)
Diarrhea	6 (19)	3 (10)	0
Nausea	4 (13)	0	0
Gastrointestinal—other	3 (10)	0	0
Peripheral edema	1 (3)	2 (7)	0
Cohort 2 (N=42)[a]			
Fatigue	7 (17)	6 (14)	2 (5)
Nausea	6 (14)	5 (12)	0
Anorexia	3 (7)	7 (17)	0
Vomiting	5 (12)	2 (5)	0
Diarrhea	3 (7)	1 (2)	0
Gastrointestinal—other	3 (7)	1 (2)	0
Peripheral edema	2 (5)	0	1 (2)
Dehydration	0	2 (5)	1 (2)

CTCAE Common Terminology Criteria for Adverse Events, Version 3.0

[a] In Cohort 1, no vomiting, anorexia, or dehydration was reported for any grade. No grade 4 toxicities were reported in either cohort

adjustments, 12 (28.6%) of the 13 had dose omissions, and 4 (9.5%) of the 13 had dose reductions. Therapy was generally well tolerated, with no grade 4 and few grade 1–3 therapy-related toxicities reported (Table 4). Two patients discontinued therapy due to adverse events: one patient developed urinary frequency/urgency, and one patient developed a rash believed possibly related to study drug.

Efficacy

Cohort 1 Of the 27 patients evaluable for PSA response, only one (4%) patient achieved a complete response; 20 (74.1%) patients had best overall tumor response of stable disease, with a median PFS of 12 weeks for the cohort. The maximum percent change of PSA from baseline per patient is illustrated in Fig. 1a.

Cohort 2 Of the 40 patients available for response, none achieved an objective response, five (11.9%) patients had a best overall response of stable disease, 28 (67%) patients had a best response of progressive disease, and nine (21%) patients did not have tumor assessment performed. The median PFS was 11 weeks (90% CI: 7.6, 11.7). The maximum percent change of PSA from baseline per patient is illustrated in Fig. 1b.

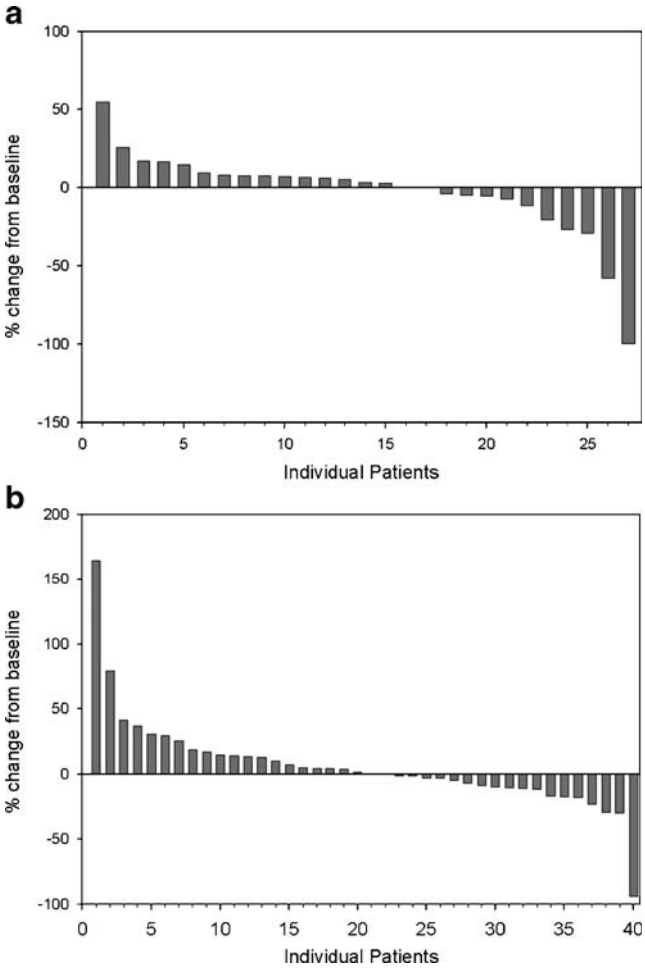

Fig. 1 PSA Response. **a** Cohort 1; **b** Cohort 2. Central laboratory data for each patient was expressed as the maximum percent change of prostate-specific antigen from baseline. Data was available for 27 patients in Cohort 1 and 40 patients in Cohort 2

Discussion

The two patient populations evaluated in this phase II study represent subsets of advanced prostate cancer that remain in need of new, clinically meaningful therapeutic interventions. Patients without overt metastatic disease who manifest PSA progression in the castrate setting are a highly heterogeneous group with a relatively long natural history [23]. Although interventions such as second-line hormonal therapy have been utilized, there is no prospective evidence that any therapy impacts on clinically meaningful endpoints such as time to development of metastatic disease or disease-specific survival [5]. Patients with castrate metastatic prostate cancer manifesting disease progression following docetaxel-based chemotherapy have a median survival of approximately 15 months, with very limited therapeutic options [17]. Patients with a reasonable performance status are sometimes managed with agents

such as mitoxantrone or re-treated with docetaxel, and while these approaches may provide a palliative benefit, no meaningful impact on disease progression or survival has been demonstrated [24].

Over the past 15 years, significant progress has been made in understanding the molecular biology of the PKC pathway, with emerging evidence of its role in a number of epithelial and hematologic neoplasms [25]. PKCβ1 and PKCβ2 are derived from a single gene by alternating splicing. They are differentially involved in cell growth, apoptosis, and cell transformation [26]. The activation of PKCβ in tumor cells results in the activation of Akt and GSK-3β leading to the transcription of vascular endothelial growth factor [12]. Although a number of PKC inhibitors have undergone clinical evaluation in a range of neoplasms, to date the clinical utility of these compounds has been limited. This is likely due in part to the complexity and tissue-specific role of PKC isozymes [27].

This exploratory two-arm phase II trial was initiated to test whether enzastaurin had demonstrable single-agent activity in two distinct prostate cancer disease subsets. Therapy in both cohorts was well tolerated. In the aggregate, there was limited evidence of single-agent activity in both disease subsets, with minimal evidence of biologic activity in the PSA-only group (response rate 4%) and essentially no activity in patients with castrate progressive metastatic disease (median PFS 11 weeks vs. 9.7 weeks historical placebo control, with no responders). The mean $C_{av,ss}$ of both enzastaurin and its metabolite observed in this study are within the range of estimates of previous oncology trials with enzastaurin administered at 500 mg/day (data on file). Based on the results observed in this trial, additional single-agent studies of enzastaurin in prostate cancer are not warranted; however, a randomized phase II trial of docetaxel with and without enzastaurin is ongoing.

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ORIGINAL REPORT

Phase I Study of Ixabepilone, Mitoxantrone, and Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Therapy: A Study of the Department of Defense Prostate Cancer Clinical Trials Consortium

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Clinical Trials repository link available on JCO.org.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Mitoxantrone plus prednisone and ixabepilone each have modest activity as second-line chemotherapy in docetaxel-refractory castration-resistant prostate cancer (CRPC) patients. Clinical noncrossresistance was previously observed.

Patients and Methods
Metastatic CRPC patients progressing during or after taxane-based chemotherapy enrolled in a phase I multicenter study of ixabepilone and mitoxantrone administered every 21 days along with prednisone. Ixabepilone and mitoxantrone doses were alternately escalated in a standard 3 + 3 design. Patients were evaluated for toxicity and disease response. Dose-limiting toxicities (DLTs) were defined as treatment related, occurring during cycle 1, and included grade 4 prolonged or febrile neutropenia, thrombocytopenia (grade 4 or grade 3 with bleeding), or ≥ grade 3 nonhematologic toxicity.

Results
Thirty-six patients were treated; 59% of patients experienced grade 3/4 neutropenia. DLTs included grade 3 diarrhea (n = 1), prolonged grade 4 neutropenia (n = 4), and grade 5 neutropenic infection (n = 1). Due to prolonged neutropenia, the highest dose levels were repeated with pegfilgrastim on day 2 of each cycle. The maximum tolerated dose in combination with pegfilgrastim was not exceeded. The recommended phase II dose is mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2 every 21 days, pegfilgrastim 6 mg subcutaneously day 2, and continuous prednisone 5 mg twice per day. Thirty-one percent of patients have experienced ≥ 50% prostate-specific antigen (PSA) declines, and two experienced objective responses. Of 21 patients treated with mitoxantrone 12 mg/m^2 plus ixabepilone ≥ 30 mg/m^2, nine (43%) experienced ≥ 50% PSA declines (95% CI, 22% to 66%).

Conclusion
These results suggest that the combination of ixabepilone and mitoxantrone is feasible and active in CRPC and requires dosing with pegfilgrastim.

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INTRODUCTION

Docetaxel improves survival for patients with metastatic castration-resistant prostate cancer (CRPC).[1,2] However, the median progression-free survival with docetaxel is approximately 6 months, and many patients with disease progression after docetaxel treatment remain in otherwise reasonable health with a good performance status.[1] No standard therapy exists for treatment of CRPC patients with progression following docetaxel therapy.

Ixabepilone and mitoxantrone are two agents that may have utility in CRPC patients whose disease has progressed after docetaxel. Ixabepilone (Ixempra; Bristol Myers-Squib, New York, NY) is a semi-synthetic epothilone analog recently approved by the US Food and Drug Administration for the treatment of chemotherapy-refractory metastatic breast cancer. Ixabepilone has demonstrated evidence of activity in taxane-resistant cell lines, as well as substantial activity in the first-line treatment of CRPC.[3,4] Similarly, mitoxantrone

(plus a corticosteroid) has demonstrated palliative activity in first-line therapy for CRPC.[5,6] We have previously reported the activity of ixabepilone or mitoxantrone and prednisone (MP) in patients with taxane-refractory CRPC.[7] Both regimens demonstrated modest activity (ixabepilone ≥ 50% prostate-specific antigen [PSA] decline in 17% of patients, MP ≥ 50% PSA decline in 20% of patients). On planned cross-over to the other agent, 11% and 27% of patients demonstrated third-line PSA responses to ixabepilone and MP, respectively, suggesting some clinical noncrossresistance between the two regimens. This has provided the rationale to test the efficacy of ixabepilone administered in combination with MP to patients with disease progression during or after docetaxel-based first-line chemotherapy. While toxicities of these two regimens are somewhat nonoverlapping, concern regarding the use of two potentially myelosuppressive regimens in elderly patients with heavy pretreatment and potential bone marrow involvement mandated cautious dose escalation.

PATIENTS AND METHODS

Study Design

This study was a multicenter, single arm, phase I dose escalation study testing the safety of ixabepilone and MP in CRPC patients with progression during or after prior docetaxel-based chemotherapy. The study was designed to alternately escalate ixabepilone and mitoxantrone for each subsequent dose cohort. A total of six dose combinations were planned as displayed in Table 1. The standard phase I escalation criteria based on the number of DLTs were applied to each dose cohort. The primary end point of the study was to determine the maximum tolerated dose of the combination. Secondary end points included overall safety and frequency of PSA declines and objective responses.

Eligibility Criteria

All patients had histologically confirmed metastatic prostate cancer. Patients were required to have progressive disease despite castrate testosterone levels and at least three cycles of prior taxane-based chemotherapy. Patients were not allowed to have received more than one prior chemotherapy regimen. For patients with measurable disease, progression was defined by Response Evaluation Criteria in Solid Tumors.[8] For patients without measurable disease, a positive bone scan and elevated PSA higher than 5 ng/mL were required. PSA evidence for progressive disease was defined by PSA Working Group 1 Consensus Criteria.[9]

All patients were required to have Eastern Cooperative Oncology Group performance status of 0 to 2, and ≤ grade 1 peripheral neuropathy (National Cancer Institute Common Toxicity Criteria, version 3.0). Hormone therapy other than luteinizing hormone-releasing hormone agonist or a stable dose of corticosteroid from prior treatment was not allowed within 4 weeks of trial enrollment. Any radiotherapy or radiopharmaceutical treatment must have been completed more than 4 weeks and 8 weeks before enrollment, respectively. All patients were required to have a cardiac ejection fraction greater than the lower limit of institutional normal. Patients with significant cardiovascular disease including congestive heart failure (New York Heart Association class III or IV), active angina pectoris, or myocardial infarction within 6 months were excluded. Patients with known active brain metastases were excluded. Required laboratory values included testosterone lower than 50 ng/dL; creatinine ≤ 1.5× upper limits of normal (ULN) or calculated creatinine clearance of 40 mL/min; ALT and AST lower than 2.5× ULN; granulocytes ≥ 2,000/mm^3; platelets ≥ 100,000/mm^3; total bilirubin lower than 1.5× ULN; and, if no bidimensionally measurable disease, PSA ≥ 5 ng/mL. Because ixabepilone is a major CYP3A4 substrate, concurrent use of moderate to strong CYP3A4 inhibitors was strongly discouraged.

This clinical trial was sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute, conducted through the Department of Defense Prostate Cancer Clinical Trials Consortium, and approved by the institutional review boards of each participating center. All patients provided written informed consent.

Table 1. Dose Escalation Schema

Dose Level	Regimen			
	Mitoxantrone (mg/m^2)	BMS-247550 (ixabepilone; mg/m^2)	Prednisone (mg PO BID)	Pegfilgrastim (mg SC on day 2)
I	8	20	5	—
II	8	25	5	—
III	10	25	5	—
IV	10	30	5	—
V	12	30	5	—
VI	12	35	5	—
Va	12	30	5	6
VIa	12	35	5	6

Abbreviations: PO, orally; BID, twice per day; SC, subcutaneously.

Treatment Plan

The dose escalation schema is depicted in Table 1. Patients were treated every 21 days. Patients were premedicated 1 hour before ixabepilone treatment with oral H1- and H2-blockers to prevent hypersensitivity reactions. For patients who developed grade 2 to 4 hypersensitivity reactions to ixabepilone, corticosteroid premedication was used with subsequent cycles. Patients received mitoxantrone intravenously over 30 minutes, followed by ixabepilone intravenously over 3 hours on day 1 of each cycle. Prednisone was given 5-mg twice daily continuously. Patients on dose levels Va and VIa received prophylactic subcutaneous pegfilgrastim on day 2. Patients had complete blood counts tested on days 8 and 15 of each cycle. Patients were treated until disease progression or unacceptable toxicity. Patients underwent imaging with chest x-ray, bone scan, and computed tomography or magnetic resonance imaging of the abdomen and pelvis at baseline and after every 3 cycles. ECG and either multiple gated-acquisition scan or echocardiogram were obtained at baseline and repeated every 3 cycles.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Three patients were enrolled at each dose level. If one of three patients experienced a dose-limiting toxicity (DLT) during the first cycle, three additional patients were enrolled at that dose level. If no additional DLTs were observed, then dose escalation proceeded. If two or more patients in a cohort experienced a DLT, then the maximum tolerated dose would be considered exceeded. DLT was defined as treatment-related toxicity occurring within the first 21 days of therapy that included ≥ grade 3 nonhematologic toxicity (excluding fatigue, alopecia, or toxicity attributed to androgen deprivation), hematologic toxicity defined as grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding, grade 4 neutropenia persisting for more than 7 days, grade 4 neutropenia associated with fever higher than 38.5C, or removal of a patient from toxicity attributable to treatment. Lymphopenia or anemia of any grade, and toxicities related to androgen deprivation therapy were excluded as DLTs.

Dose modifications were defined according to protocol. Dosages were reduced for day 1 neutrophil count lower than 1,500/mm^3 or platelet count lower than 75,000/mm^3, neutrophil count lower than 500/mm^3 for more than 7 days, neutrophil count lower than 500/mm^3 associated with fever, platelet count lower than 25,000/mm^3, or platelet count lower than 50,000/mm^3 associated with bleeding, and any ≥ grade 3 nonhematologic toxicity related to therapy. Grade 2 or 3 neurotoxicity required ixabepilone dose reduction. Grade 4 and recurrent grade 3 neurotoxicity required ixabepilone discontinuation. Mitoxantrone was discontinued if the ejection fraction decreased below the institutional lower limit of normal and declined by ≥ 15%. For each dose reduction, ixabepilone dose was reduced by 5 mg/m^2, and mitoxantrone dose was reduced by 2 mg/m^2. Patients were removed from treatment if more than two dose reductions were required or if there was a treatment delay of longer than 21 days due to toxicity. Patients were not treated with prophylactic

antibacterials, and granulocyte growth factor for asymptomatic neutropenia on dose levels I to VI. Secondary prophylaxis with growth factors for recurrent neutropenic infection was allowed in dose levels I to VI.

Statistical Considerations

Successive cohorts of patients were accrued to determine the maximum tolerated dose that resulted in lower than 33% DLTs with the combination of ixabepilone and MP. At least six patients were treated at the maximum dose to increase the likelihood that the risk of a DLT was lower than 33%. Secondary objectives were to obtain initial estimates of response to study therapy based on PSA Working Group 1 criteria and objective responses by RECIST in patients with measurable disease.[8,9]

RESULTS

Patient Characteristics

Between July 2006 and February 2008, 36 patients were enrolled at four participating centers (Table 2). The median age of patients was 66. Seventy-one percent of patients had a Gleason score of 8 to 10. Sixty-four percent of patients had an ECOG performance status of 1 to 2, while 36% had an ECOG performance status of 0. The median lactate dehydrogenase, alkaline phosphatase, and hemoglobin were 313 U/L, 142 U/L, and 11.9 g/dL. The median number of prior chemotherapy cycles was 8.5. Forty-seven percent of patients had experienced a PSA response to prior taxane-based therapy by PSA Working Group 1 criteria. Twenty-three patients (64%) progressed on docetaxel therapy by PSA criteria, nine (25%) progressed on docetaxel therapy in bone and/or soft tissue, two (5.5%) stopped docetaxel therapy for toxicity, and two (5.5%) stopped docetaxel therapy with stable disease after completing a course of chemotherapy. The majority of patients received no intercurrent therapy between docetaxel treatment and enrollment on trial. Two patients received other investigational therapy after docetaxel before enrollment (vorinostat and tandutinib; Millenium Pharmaceuticals, Cambridge, MA), and two other patients received palliative radiotherapy.

Table 2. Patient Characteristics (N = 36)

Characteristic	No.	%
Median age, years	66	
Range	36-79	
Gleason score	35	
6-7	10	
8-10	25	
ECOG PS		
0	13	
1-2	23	
Median PSA, ng/mL	236.93	
Range	12.8-7,167	
Mean No. of prior chemotherapy cycles	8.5	
Range	3-80	
Prior chemotherapy regimens		
Docetaxel	25	
Docetaxel + bevacizumab/placebo	4	
Docetaxel + sunitinib	2	
Docetaxel + estramustine	3	
Docetaxel + valatinib	1	
Docetaxel + diethylstilbestrol	1	
Prior chemotherapy best response		
PSA decline ≥ 50%	17	
Progressive disease	12	
Stable disease	7	
Reason for discontinuing docetaxel		
PSA progression only	23	
Bone progression	3	
Soft tissue progression	5	
Both bone and soft tissue progression	1	
Toxicity	2	
Completed therapy, stable disease	2	
Interval between docetaxel and study therapy, days		
≥ 60	25	
< 60	11	
Baseline laboratory tests		
Median LDH, U/L	313	
Range	118-1,046	
Median alkaline phosphatase, U/L	142	
Range	37-780	
Median hemoglobin, g/dL	11.9	
Range	8.4-14.1	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.

Dose Escalation and DLT

A total of 178 cycles of treatment were administered to 36 patients. No DLTs were observed in the first three cohorts (Table 3). At dose level IV (mitoxantrone 10 mg/m^2, ixabepilone 30 mg/m^2) one patient experienced grade 4 neutropenia lasting longer than 7 days leading to cohort dose expansion. No further DLTs were observed at this dose level. At dose level V (mitoxantrone 12 mg/m^2, ixabepilone 30 mg/m^2), one patient experienced grade 3 diarrhea, leading to cohort expansion. An additional event of grade 4 neutropenia lasting more than 7 days was identified only after dose escalation had occurred to dose level VI. At dose level VI (mitoxantrone 12 mg/m^2, ixabepilone 35 mg/m^2), one patient experienced dose-limiting grade 4 neutropenia lasting longer than 7 days, leading to cohort expansion. In the cohort expansion, a second patient on dose level VI also experienced grade 4 neutropenia lasting longer than 7 days, constituting DLT, and accrual was stopped to this cohort. Based on these toxicities, the study was amended to repeat dose levels V and VI with the addition of pegfilgrastim 6 mg subcutaneously on day 2 (dose levels Va and VIa). No DLTs were observed on dose level Va (mitoxantrone 12 mg/m^2, ixabepilone 30 mg/m^2, pegfilgrastim 6 mg subcutaneous). One patient treated on dose level Va was inadvertently treated with the dose level VIa dose of ixabepilone (5 mg higher than planned) for cycle 1, and was replaced in the dose escalation. As this dose level had been previously tested without pegfilgrastim, the patient was included in the overall toxicity and response reporting. One patient on dose level VIa (mitoxantrone 12 mg/m^2, ixabepilone 35 mg/m^2, pegfilgrastim 6 mg subcutaneous) died of neutropenic infection leading to respiratory and renal failure in the setting of progressive disease during cycle 1 of treatment. That patient was also receiving concomitant therapy with verapamil, a moderate CYP3A4 inhibitor. Dose level VIa was expanded to six patients, and no further DLTs were observed. The maximum tolerated dose with the combination of ixabepilone and mitoxantrone was not exceeded in this study, but further dose escalation was not undertaken, as the study plan was to reach therapeutic dose levels for each drug (mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2) and not escalate further. Furthermore, the treatment-related

Table 3. DLTs (cycle 1 only) and Responses

Dose Level	DLT Frequency	DLTs	PSA Declines ≥ 50%/ Total Patients	Objective Responses/ Assessable Patients
I	0/3	—	0/3	0/2
II	0/3	—	0/3	0/1
III	0/3	—	1/3	0/2
IV	1/6	Prolonged grade 4 neutropenia	1/6	1/4
V	2/6	Grade 3 diarrhea; prolonged grade 4 neutropenia	2/6	1/5
VI	2/5	Prolonged grade 4 neutropenia × 2	3/5	0/3
Va	0/4		2/4	0/2
VIa	1/6	Grade 5 neutropenic infection	2/6	0/1

Abbreviation: DLT, dose-limiting toxicities.

death on the highest dose level suggested that further dose escalation was not warranted. Based on the observed DLTs, the recommended phase II dose is mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2 day 1, pegfilgrastim 6 mg on day 2, and prednisone 5 mg twice daily continuously.

Overall Toxicity

As anticipated, hematologic toxicity was frequently observed (Table 4). Grade 3 neutropenia was observed in 28% of patients, and grade 4 neutropenia was observed in 31% of patients. Grade 4 neutropenia lasting longer than 7 days was observed in 11% of patients. Grade 3/4 neutropenia was observed in 33% of all treatment cycles. Grade 3 thrombocytopenia and grade 3 anemia were infrequent (6% and 8% respectively), and no patients experienced grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding.

Nonhematologic toxicity related to study therapy is detailed in Table 5. Cardiovascular toxicity included two patients with grade 2 asymptomatic decreased left ventricular ejection fraction (to 40% to 50%), and two patients with atrial fibrillation (one grade 2, another grade 3). Grade 3 motor neuropathy was observed in one patient, grade 2 motor neuropathy was observed in one patient, and grade 2 sensory neuropathy was observed in one patient.

Response Evaluation

Anticancer activity was assessed as a secondary end point of this study. Partial objective RECIST-defined responses were observed in two of 20 patients with measurable disease: one on dose level IV and one on dose level V. In addition, 11 patients (31%) experienced confirmed PSA declines ≥ 50% (Table 3 and online-only Appendix Fig A1). Of the 21 patients who received the US Food and Drug Administration–approved mitoxantrone dose of 12 mg/m^2 (dose levels V, Va, VI, and VIa), nine patients (43%) experienced confirmed PSA declines ≥ 50% (Fig 1; 95% CI, 22% to 66%). For responders, the median time to progression was 5.3 months (range, 3.0 to 11.1).

Table 4. Frequency of Grade 3 and 4 Hematologic Toxicity Across All Dose Levels and All Cycles

	Grade 3		Grade 4	
Toxicity	No.	%	No.	%
Neutropenia	10	28	11	31
> 7 days	9	25	4	11
Febrile neutropenia	1	3	—	—
Lymphopenia	12	33	2	6
Leukopenia	10	28	6	17
Thrombocytopenia	2	6	—	—
Anemia	3	8	—	—

DISCUSSION

While docetaxel chemotherapy is associated with an overall survival benefit for patients with castration-resistant prostate cancer, the median time to progression remains short, and overall survival remains fewer than 2 years. Recently reported data demonstrated that satraplatin did not provide a survival benefit when compared with prednisone alone in CRPC patients previously treated with chemotherapy.[10] Thus, the exploration of new therapeutic approaches for these patients is clearly warranted.

In a previously reported randomized phase II trial, ixabepilone and MP appeared to have clinical noncrossresistance as second- and third-line therapy for CRPC.[7] Several patients who progressed on one arm and crossed over to the other therapy demonstrated responses. Based on these data, the current study evaluated the safety and tolerability of the combination of ixabepilone and MP as second-line chemotherapy in patients with metastatic CRPC who had progressed during or after a single taxane-based chemotherapy regimen.

This study has demonstrated that mitoxantrone and ixabepilone can generally be safely administered in combination at doses that have demonstrated single-agent activity in CRPC. The recommended phase II dose is mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2 administered intravenously every 21 days, along with prednisone 5 mg orally twice per day continuously. Treatment was well tolerated in most patients. However, treatment at these dose levels required pegfilgrastim to prevent prolonged neutropenia. High rates of neutropenia have been observed with mitoxantrone-based chemotherapy in prostate cancer. For example, grade 3/4 neutropenia was observed in 59% of patients treated with mitoxantrone, without a concomitant high incidence of neutropenic infections or morbidity.[5] The low frequency of febrile neutropenia may be explained by the relatively low frequency of severe mucositis observed with mitoxantrone. In this phase I study, no patients experienced grade 3 or 4 mucositis.

Table 5. Grade 2 and Higher Treatment-Related Maximal Nonhematologic Toxicity, All Dose Levels, and All Cycles

	Grade					
	2		3		4	
Toxicity	No.	%	No.	%	No.	%
Alopecia	1	3	—	—	—	—
Anorexia	2	6	—	—	—	—
ARDS	1	3	—	—	—	—
Atrial fibrillation	1	3	1	3	—	—
Bone pain	2	6	—	—	—	—
Chest pain	1	3	—	—	—	—
Dehydration	—	—	1	3	—	—
Diarrhea	1	3	1	3	—	—
Dizziness	1	3	—	—	—	—
Dyspepsia	1	3	—	—	—	—
Dyspnea	1	3	—	—	—	—
Edema limbs	1	3	—	—	—	—
Fatigue	11	31	—	—	—	—
Febrile neutropenia	1	3	—	—	—	—
Fever	1	3	—	—	—	—
Hot flashes	1	3	—	—	—	—
Infection	1	3	—	—	2	6
Muscle weakness	1	3	1	3	—	—
Nausea	3	8	—	—	—	—
Pain	1	3	—	—	—	—
Peripheral motor neuropathy	1	3	1	3	—	—
Peripheral sensory neuropathy	1	3	—	—	—	—
Phlebitis	1	4	—	—	—	—
Pleural effusion	1	4	—	—	—	—
Pneumonia	1	3	2	6	—	—
Reduced LVEF	2	6	—	—	—	—
Renal failure	—	—	—	—	1	3
Syncope	—	—	1	3	—	—
Taste alteration	2	6	—	—	—	—
Vomiting	2	6	1	3	—	—
Weight loss	2	6	—	—	—	—

Abbreviations: ARDS, adult respiratory distress syndrome; LVEF, left ventricular ejection fraction.

While further dose escalation was formally possible beyond doses of mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2, due to concerns of broad applicability of the regimen to the general population of CRPC patients, further dose escalation was not pursued.

Neurotoxicity was not frequently observed in this study despite the sequential use of two potentially neurotoxic agents (docetaxel and ixabepilone). Only 12% of patients experienced grade 2 or greater neuropathy. These data are consistent with the previous study of ixabepilone monotherapy after taxanes in CRPC.[7] Patients with preexisting grade 2 or higher neuropathy were excluded from participation in this trial. These data are also similar to what has been observed in taxane-refractory metastatic breast cancer patients treated with ixabepilone.[11,12] As a result, it may be that these criteria selected for a patient population less susceptible to neuropathy. Furthermore, variations in assessment of toxicity between different physicians and different institutions may result in under-reporting of grade 3 neuropathy.

Although efficacy was not a primary end point of this study, the frequency of PSA declines observed with the combination is intriguing. In patients who received treatment on this study with the US Food and Drug Administration–approved doses of mitoxantrone, the PSA response frequency was 42%, while the PSA response rate for salvage mitoxantrone and prednisone has been reported to be 20%.[7] The PSA response frequency in first-line mitoxantrone studies ranges from 19% to 32%.[1,2,5] While the numbers of patients in this study are small, these results indicate that the addition of ixabepilone to MP may result in at least additive efficacy. While PSA declines are an intermediate end point and not a direct measure of clinical benefit, the PSA Working Group Consensus Criteria were developed precisely to screen for the activity of cytotoxic regimens in men with metastatic CRPC. The preliminary activity demonstrated in this study suggests that this regimen is worthy of further evaluation. The DOD Prostate Cancer Clinical Trials Consortium is testing this regimen in ongoing phase II study.

One potential weakness of this study may result from patient selection resulting in a group of patients not accurately reflecting the distribution of CRPC patients in the community. In fact, in an earlier study of mitoxantrone versus ixabepilone, such selection was mandated by virtue of an eligibility requirement of progression while on docetaxel or within 60 days of the last docetaxel dose. This study had no such restrictions, and, in fact, 31% of patients accrued to this study developed progressive disease more than 60 days after

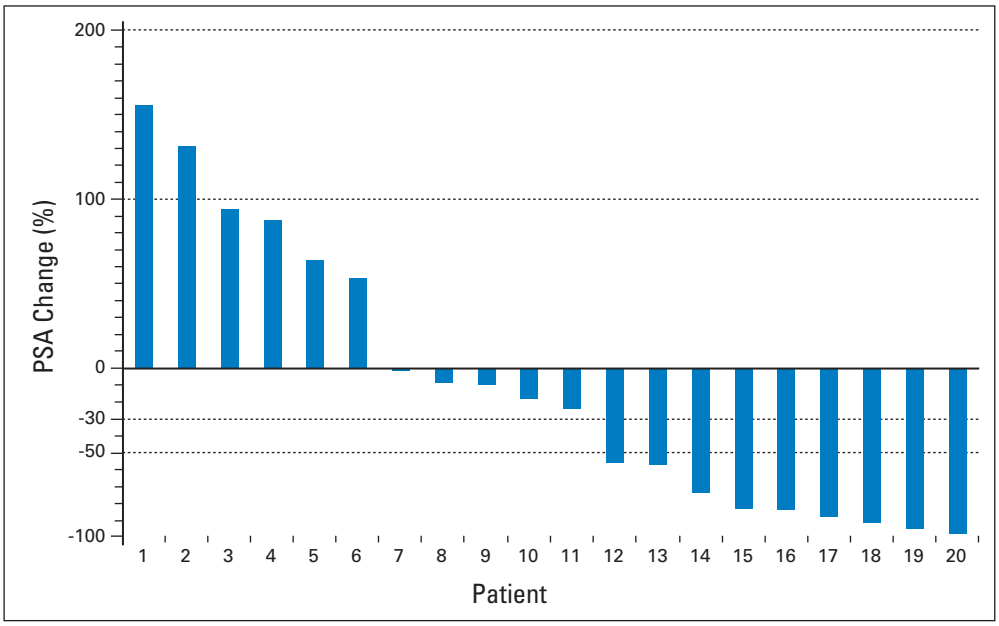

Fig 1. Prostate-specific antigen (PSA) waterfall plot of maximum PSA declines of the 21 patients who received the US Food and Drug Administration–approved mitoxantrone dose of 12 mg/m^2 (dose levels V, Va, VI, and VIa). Nine patients (43%) experienced confirmed PSA declines of at least 50% (95% CI, 22% to 66%).

the last docetaxel dose. It is possible that some of these patients might have responded to rechallenge with docetaxel. While this difference may result in inadvertent selection of "better" patients for this study, it also reflects the broad distribution of taxane pretreated patients in the community.

A second potential weakness involving careful patient selection at a single specialized center is somewhat addressed by the multicenter participation in this trial. Nevertheless, this study, conducted in four high volume prostate cancer tertiary referral centers, demonstrates that combination chemotherapy for second-line chemotherapy for CRPC is feasible with these agents.

In summary, the combination of ixabepilone and mitoxantrone with pegfilgrastim is safe and feasible in metastatic CRPC patients who have developed progressive disease despite docetaxel-based therapy. Furthermore, this regimen has demonstrated sufficient activity to warrant phase II testing.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix AA

Invest New Drugs
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PHASE II STUDIES

Phase II study of Cilengitide (EMD 121974, NSC 707544) in patients with non-metastatic castration resistant prostate cancer, NCI-6735. A study by the DOD/PCF prostate cancer clinical trials consortium

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Summary *Background*: Integrins mediate invasion and angiogenesis in prostate cancer bone metastases. We conducted a phase II study of Cilengitide, a selective antagonist of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins, in non-metastatic castration resistant prostate cancer with rising PSA. *Methods*: Patients were observed for 4 weeks with PSA monitoring, and then treated with 2,000 mg IV of cilengitide twice weekly until toxicity/progression. PSA, circulating tumor cells (CTCs) and circulating endothelial cells (CECs) were monitored each cycle with imaging performed every three cycles. Primary end point was PSA decline by ≥50%. Secondary endpoints were safety, PSA slope, time to progression (TTP), overall survival (OS), CTCs, CECs and gene expression. *Results*: 16 pts were enrolled; 13 were eligible with median age 65.5 years, baseline PSA 8.4 ng/mL and median Gleason sum 7. Median of three cycles was administered. Treatment was well tolerated with two grade three toxicities and no grade four toxicities. There were no PSA responses; 11 patients progressed by PSA after three cycles. Median TTP was 1.8 months and median OS has not been reached. Median pre- and on-treatment PSA slopes were 1.1 and 1.8 ng/mL/month. Baseline CTCs were detected in 1/9 patients. CTC increased (0 to 1; 2 pts), remained at 0 (2 pts) or decreased (23 to 0; 1 patient) at progression. Baseline median CEC was 26 (0–61) and at progression, 47 (15–148). Low cell counts precluded gene expression studies. *Conclusions*: Cilengitide was well tolerated but had no detectable clinical activity. CTCs are of questionable utility in non-metastatic prostate cancer.

Keywords EMD 121974 · Cilengitide · Non-metastatic castration resistant prostate cancer

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Introduction

Non-metastatic castration resistant prostate cancer (CRPC) is a distinct disease state that is characterized by rising PSA despite androgen deprivation therapy without evidence of distant metastases. This clinical state could last a few years and presents an opportunity to intervene with therapy designed to delay progression to metastatic disease [1]. Delay/prevention of clinical systemic metastasis is a clinically meaningful objective.

Formation of bone metastasis is a multi-step process that involves invasion of the vasculature by tumor cells, cell migration to and adhesion at distant bone sites, angiogenesis and tumor growth [2, 3]. Interactions between tumor and endothelial cells on one hand and the extracellular matrix (ECM) components (such as vitronectin, fibronectin and osteopontin) on the other mediate several of these steps. Interactions of the ECM with tumor cells and endothelial cells are dependent on a class of transmembrane cell surface receptors called integrins.

The role of integrins in prostate cancer metastases

Integrins transduce signals between the ECM and the intracellular cell signaling pathways of endothelial or tumor cells in both directions[4]. Structurally, they are heterodimers consisting of an alpha and a beta subunit. At least 18 alpha and eight beta subunits have been identified with more than 24 unique integrin heterodimers recognized so far[5].

Integrins play important roles in cell migration, adhesion, invasion, proliferation, survival and angiogenesis of epithelial neoplasms [4, 6, 7] . $\alpha_v\beta_3$ is expressed in prostate cancer cells but not in normal prostate cells[8]. Prostate cancer cell lines derived from bone metastases uniformly express $\alpha_v\beta_3$[9]. Preclinical studies show that $\alpha_v\beta_3$ integrin mediates the adhesion of prostate cancer cells to ECM components of the bone such as osteopontin [10, 11]. α_v integrins also promote survival of prostate cancer cells in bone[12] and siRNAs directed against α_v integrins induce apoptosis of PC3 prostate cancer cells in bone[13]. $\alpha_v\beta_3$ also mediates osteopontin (ECM component) triggered proliferation of castration resistant prostate cancer cells in bone[14]. Bone turnover by osteoblasts and osteoclasts involves interaction of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ with osteopontin and bone sialoprotein [15, 16]. Blockade of $\alpha_v\beta_3$ reduces osteoclast recruitment and bone lysis initiated by metastatic cancer cells[17]. Thus, integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ promote metastasis of prostate cancer cells to bone in each step of the metastatic process [4, 5, 18].

Endothelial cells when activated by tumor secreted cytokines express $\alpha_v\beta_3$ [19]. A crucial role of $\alpha_v\beta_3$ in activated endothelial cells is to inhibit apoptosis by up-regulating NF-kB activity [20, 21]. Antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ block endothelial cell proliferation and differentiation induced by fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF) in cell lines, chicken chorioallantoic membrane (CAM) and severe combined immunodeficient (SCID) mice [22]. Novel agents that target integrins have shown promising clinical activity in glioblastoma multiforme [23].

Cilengitide Cyclo-l-Arg-Gly-l-Asp-d-Phe-N (Me) l-Val; (Merck KGaA, Darmstadt, Germany) is a cyclic pentapeptide and RGD mimetic that selectively and competitively antagonizes ligand binding to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in vitro. Cilengitide or EMD121974 inhibited proliferation and increased apoptosis in cell lines and caused tumor regression in cell culture [24, 25]. It blocks angiogenesis stimulated by VEGF and FGF in a 3-D gel of bovine endothelial cells [26]. Cilengitide also inhibited $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in CAM and in orthotopic models of human melanoma, medulloblastoma and glioblastoma (GBM) in nude and SCID mice [27, 28].

In a phase I clinical trial of cilengitide in advanced solid tumors, twice-weekly infusions of cilengitide were administered to 37 patients continuously at doses from 30 mg/m^2 up to 1600 mg/m^2 in 4 week cycles [29]. In another phase I trial, 20 patients were treated at two doses (600 and 1200 mg/m^2 on the same schedule as the above study) [30]. In both studies, no dose limiting toxicity was observed. The terminal half-life at all doses in both studies was around 4 h. C_{max} concentrations achieved in plasma at 120 mg/m^2 were comparable to tumor inhibitory plasma levels in mice. No hematological or grade 3/4 non-hematologic toxicity were reported. In the phase I component of two NCI sponsored studies (NCT00022113 and NABTT-9911/ NCT00006093) of cilengitide given intravenously twice weekly, no dose limiting toxicity was observed at doses as high as 2400 mg/m^2.

Given the critical role of integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ in promoting angiogenesis and bone metastasis in prostate cancer and the preclinical and clinical safety profile of cilengitide we conducted a single-arm multi-center NCI sponsored phase II study of single agent cilengitide (NCI-6735) in non-metastatic rising PSA-only castration-resistant prostate cancer. The dosing and schedule were based on earlier phase I trials of cilengitide and phase II trials in advanced melanoma (00082875 MDACC 2004) and recurrent GBM (NCT00093964).

Patients and methods

Patients were eligible if they had a histologic or cytologic diagnosis of prostate cancer with no evidence of metastatic

disease or local progression on radiologic imaging (Bone scan, CT/MRI of abdomen and pelvis) and had three consecutive rising levels of prostate specific antigen (PSA) at a minimum of one week intervals with the last of those values ≥2 ng/mL. Patients had to have PSA progression despite androgen deprivation therapy and anti-androgen withdrawal (≥ 4 weeks off flutamide; ≥ 6 weeks off bicalutamide or nilutamide). ECOG performance status of 0–2 and adequate organ and hematologic function were required (ANC ≥1500/uL, platelets ≥100,000/uL, serum creatinine ≤1.5×upper limits of normal, normal bilirubin and LFTs ≤2.5×upper limits of normal). Patients who had not had orchiectomy were required to continue on LHRH agonist therapy with a castrate range testosterone level. Patients on stable doses of steroids or megace for longer than 1 month continued on the same doses. Patients had to be >4 weeks from major surgery and prior systemic anti-cancer therapy. No previous treatment with cilengitide was allowed. Continuing bisphosphonate use was permitted if on stable doses for >6 weeks prior to registration on protocol but was not allowed to be initiated while on the study. No concurrent herbal or food supplements (such as PC-SPES or saw palmetto) other than a daily multivitamin were allowed during the study. Patients with a second active malignancy (less than 2 years from completion of therapy or with current evidence of disease) were excluded except for superficial bladder cancer or non-melanomatous skin cancer. Men of reproductive potential had to agree to use effective contraception. All patients on the study signed an informed consent approved by the institutional review board at the respective participating institution prior to study entry. This Cancer Therapy Evaluation Program (CTEP) sponsored trial was conducted by the Department of Defense-Prostate Cancer Clinical Trials Consortium.

Treatment plan

Patients had a lead-in observation period of 4 weeks with PSA measured at 2 weeks and 4 weeks (Fig. 1). Treatment with cilengitide began after the 4 weeks lead-in period. Cilengitide was administered at a starting dose of 2000 mg intravenously over 1 h twice weekly each week in 4 week cycles without any planned breaks between cycles. Grade 4 hematologic or grade 3 or 4 non-hematologic toxicities by NCI CTCAE version 3.0 necessitated holding the drug until resolution of toxicities to grade ≤1 and re-starting treatment at −1 dose level (1600 mg/dose). Recurrent serious toxicity triggered reduction to −2 dose level (1200 mg/dose) after resolution to ≤1 grade. Therapy was stopped for a third occurrence of toxicity of that grade. Treatment could be interrupted for a maximum of two consecutive doses or four doses in a 12-week period. Based on phase I studies of cilengitide that demonstrated no dose-toxicity relationship

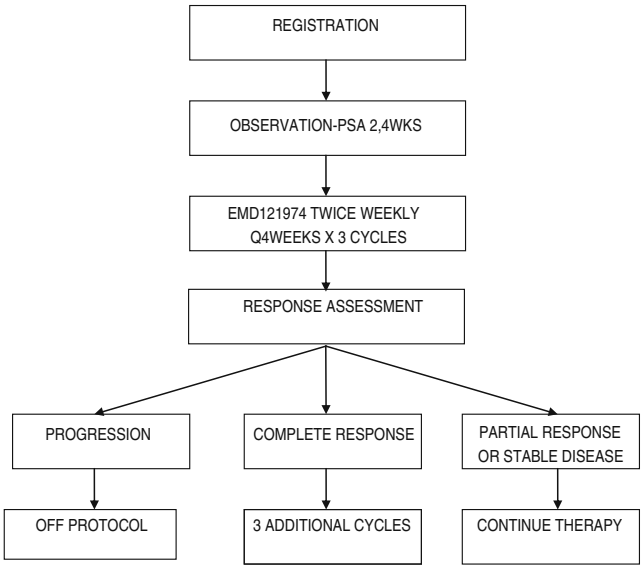

Fig. 1 Treatment Schema

and no DLT at doses up to 2000 mg, dosing was not based on body weight or surface area [23, 29]. Cilengitide was provided by DCTD, NCI.

Duration of therapy and monitoring

In the absence of toxicity, patients were treated on protocol for a minimum of three cycles (12 weeks) prior to response assessment in order to permit an adequate evaluation of the effect of the investigational agent. Patients were evaluated for toxicity and had PSA measured each cycle. Imaging with bone scan and CT or MRI abdomen/pelvis was performed every three cycles. Beyond the first three cycles, treatment was stopped when any one of the following occurred: clinical or PSA progression, after three additional cycles beyond complete response, recurrence of serious toxicity in spite of dose reduction to −2 dose level and maximally allowed dose interruptions, patient preference or worsening of the patient's general medical condition that precluded further treatment in the judgment of the investigator. The PSA value at the end of the 4 week lead-in period prior to the first dose was considered the baseline PSA.

End points and statistical design

Complete response was defined as PSA <0.2 ng/mL, partial response as decline in PSA by 50% from baseline and progression as ≥25% rise in PSA over baseline or nadir whichever was lower[31]. PSA responses and progression needed confirmation by a successive PSA at least 4 weeks later. Patients not meeting criteria for either response or progression were considered to have stable disease. Patients

with partial response or stable disease by PSA criteria with no evidence of objective disease progression continued treatment with cilengitide until criteria for halting therapy were met.

The primary end-point of the study was PSA response rate (complete and partial response) in patients treated with single-agent cilengitide in non-metastatic castration-resistant prostate cancer. Secondary endpoints were safety of cilengitide, changes in PSA slope with treatment, response duration, time to progression and survival. For calculation of pre-treatment PSA slope, at least three PSA values including the lead-in observation period values on weeks 2 and 4 (baseline) were included. For on-treatment PSA slope, the baseline PSA and all PSA values in the first 6 months of treatment with cilengitide were considered. The study was designed to accrue 32 patients to provide 90% power at the 10% significance level to detect a difference between a 5% versus a 20% response rate. If four or more PSA responses were seen in this population, further study would be undertaken. To prevent against excess toxicity, if ≥3 of the first 12 patients experienced a high-grade non-hematologic toxicity (grade 3 and/or 4) excluding alopecia, nausea or vomiting, the trial would stop early. All of the eligible patients (with the exception of those who received no study medication) are included in the main analysis of the response rate. Survival and time to progression was determined by Kaplan-Meier analysis.

Correlative biology studies

In the absence of objective disease in non-metastatic CRPC, we planned to evaluate circulating tumor and endothelial cells (CTC and CEC). Correlatives included enumeration of CTC using the CellSearch assay (Veridex, Huntington Valley, PA) and CEC using the CellTracks reagents (Veridex, formerly Immunicon Corp.). All CTC and CEC enumeration was performed at Immunicon Corp. and results were communicated to the study authors. RNA isolation was performed from CTCs and CECs from blood collected at baseline and the beginning of each cycle. Analyses included serial enumeration of CTCs and CECs in study patients, comparison of CTC/CEC numbers between patients, and microarray genotyping of CTCs/CECs.

Results

Baseline characteristics

Between January 2005 and May 2007, 16 patients were registered to the protocol at six centers. The protocol was closed due to lack of any PSA response coupled with slow accrual. 1 patient progressed clinically before any treatment and was not included in the toxicity or efficacy analysis. Two patients who received study drug were deemed ineligible as they did not meet entry PSA criteria of three consecutive rises in PSA but were included in the toxicity analysis. Table 1 describes the baseline demographic and clinical data of the 13 eligible patients. Median age was 65.5 years, median baseline PSA at registration was 8.4 with a range of 2.2 to 77, Gleason sum was seven in 46.2% and 8–9 in another 38.5%, and median Karnofsky performance score was 90 (range, 80–100). Six patients had undergone prior radical prostatectomy and five had undergone definitive radiation treatment. Three patients each had received salvage and adjuvant radiation therapy. Median time since hormone initiation for the 13 eligible patients was 4.7 years (range, 1–10.6 years). Median pre-treatment PSA slope was 1.1 ng/mL/month.

Efficacy and survival

Patients were treated for a median of three cycles (range 3–8) with cilengitide. There were no PSA responses; two patients had stable disease (SD) at 12 weeks (Fig. 2) and 11 patients had progressed by PSA criteria (two by imaging also) at first assessment after three cycles. Median on-treatment PSA slope was 1.8 ng/mL/month (not significantly different from pre-treatment slope) (Fig. 2). Time to PSA progression was 1.8 months (95% CI: 0.9–2.8). All patients are off protocol therapy. With a median follow-up of 3.1 years (range, 16 months –5 years), median overall survival has not been reached for the cohort; 5 of 13 (38%) evaluable patients have died.

Treatment related toxicity

Toxicity was evaluated by NCI-CTCAE (ver. 3) criteria in all 15 treated patients including the two ineligible patients. Therapy was tolerated very well with no grade 4 or higher adverse events reported (Table 2), There were two grade 3 (atrial fibrillation) and three grade 2 adverse events (dyspnea, lymphopenia and osteonecrosis). The patient who developed osteonecrosis was not on bisphosphonates when he was diagnosed with avascular necrosis of the femoral head. There were 22 grade 1 adverse events. Dose reduction to −1 dose level was needed in one patient (atrial fibrillation).

Correlative analysis

In patients tested at baseline for CTCs (n=9), only one had any CTCs (range 0–23) reflecting the relative paucity of CTCs. For those with CTC data at progression (n=5), CTC increased from 0 to 1 (2 patients), remained at 0 (2 pt) and decreased

Table 1 Baseline characteristics of eligible patients (n=13)

Median Age (range)	65.5 yrs (53.8–78.1)
Median Karnofsky Performance Score (range)	90 (80–100)
Median baseline PSA (range)	8.4 (2.2–77)
Gleason sum(%) 6	2 (15.4%)
7	6 (46.2%)
8	2 (15.4%)
9	3 (23.1%)
Prior Radiation to prostate	11
Definitive	5
Adjuvant	3
Salvage	3
Radical Prostatectomy	6
No Local Treatment Modality	2
Median time since ADT initiation (range)	4.7 yrs (1–10.6)

from 23 to 0 (1 pt). In patients with baseline CEC data (n=10), median CEC number was 26 (range 0–61). 8 patients had serial CEC counts. At progression (n=7), median CEC was 47 (range 15–148). Low cell counts and RNA yield precluded correlative gene expression studies. The trend of CECs on treatment is shown in Fig. 3. The significance of the transient increase in CECs on treatment is unclear.

Discussion

Routine PSA measurement after definitive local treatment and use of early androgen deprivation therapy have resulted in non-metastatic castration resistant prostate cancer disease state which is characterized by rising levels of PSA despite castrate levels of testosterone without other evidence of disease[32]. On the control arms of two separate randomized phase III trials evaluating atrasentan and zoledronic acid in non-metastatic CRPC patients, the median time to metastases was 25 and 30 months respectively[1, 33]. Non-metastatic CRPC offers a potential therapeutic window to decrease morbidity from CRPC by delaying or preventing systemic metastases yet few trials have been conducted in this stage due to the substantial challenges posed by the lack of measurable disease. However, the natural history of non-

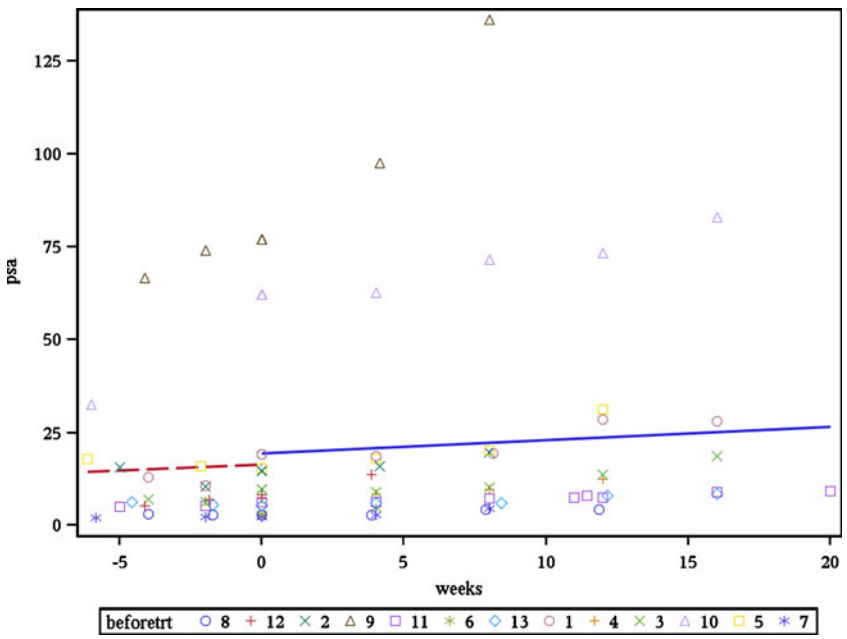

Fig. 2 PSA velocity before and after treatment with Cilengitide in evaluable patients (n=13). The broken and solid lines represent median pre-treatment and post-treatment PSA velocity respectively. Treatment with Cilengitide started at week 0. Individual PSA values for all 13 eligible patients are shown as a scatter plot

Table 2 Treatment related adverse events[a]

Adverse Event	Grade	Number
Arthritis	1	2
Increased aspartate aminotransferase	1	1
Constipation	1	1
Diarrhea	1	1
Dry eye syndrome	1	1
Edema	1	1
Fatigue	1	4
Flushing	1	1
Headache	1	1
Decreased hemoglobin	1	2
Hyperglycemia NOS	1	1
Hyperglycemia	1	1
Hyponatremia	1	1
Memory impairment	1	1
Nausea	1	1
Rash (desquamating)	1	1
Toothache	1	1
Dyspnea	2	1
Lymphopenia	2	1
Osteonecrosis	2	1
Atrial fibrillation	3	2

[a] Includes all grade 1 and above toxicities considered unknown, possible, likely or probably related to Cilengitide

metastatic CRPC is variable with greater PSA velocity and absolute PSA value predicting a more aggressive clinical course [1]. A risk adapted approach defined by such factors or other biomarkers including CTCs would certainly optimize clinical trial design in this setting.

In the absence of a control arm, a lead-in period of observation was proposed to utilize each patient as his own control by analyzing changes in PSA slope before and on treatment. We hypothesized that CTC and CEC changes could reflect disease activity and also provide a method of performing gene expression studies to verify drug activity on the intended target (the integrin pathway).

In this trial, there was no evidence of activity of Cilengitide as a single agent in this setting. There are several possible explanations for the result. It is possible that integrin mediated cell signaling was not abrogated adequately. Our ability to verify if this indeed was the case and detect drug effect on the intended target was hampered by the paucity of CTCs for the planned correlative analyses. In retrospect, CTCs (as assayed by the Veridex CellSearch test) were not ideal correlates for this trial as they are infrequently detected in the non-metastatic setting [34–36]. Though CTCs have been shown to be prognostic [37] and possibly predictive of a survival benefit with treatment in metastatic CRPC [38, 39], CTC number appears to be dependent on the tumor burden [35, 40]. CTCs are detected more frequently and at higher numbers per patient in metastatic prostate cancer. In one study, >65% patients had ≥5 CTCs/7.5 ml blood [41]. In contrast, only 14% of patients with localized epithelial cancer have ≥2

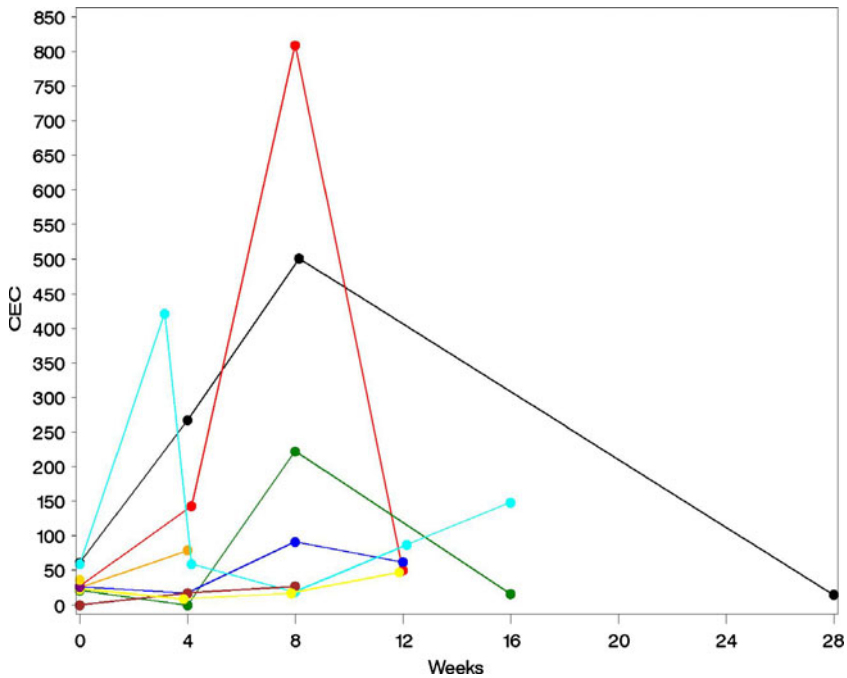

Fig. 3 Circulating endothelial cells on treatment (0 weeks indicates start of treatment)

CTCs/7.5 ml. This difference becomes especially relevant when gene expression studies are planned on CTCs as ≥ 100 CTCs per patient were necessary in one study to perform such studies [42]. CTCs by currently approved assays are of questionable value in non-metastatic prostate cancer due to low sensitivity. Methods of enrichment for CTCs or alternative techniques of detection could prove promising in non-metastatic CRPC[43].

CECs have been investigated as surrogates for angiogenesis and as prognostic and predictive biomarkers [44, 45]. However, experience with CECs in prostate cancer is more limited than with CTCs. One study of CECs in metastatic prostate cancer treated with docetaxel found CEC declines after 2–5 weeks of treatment but not baseline CECs to be of prognostic value[39].

It is conceivable that integrin signaling was indeed blocked (suggested by the activity of Cilengitide at similar doses in GBM and modest activity in metastatic CRPC[46]) but was not adequate in and of itself in non-metastatic CRPC. The presence of multiple integrin molecules and other pro-angiogenic pathways provides significant redundancy in intracellular signaling pathways. Compensatory pathways could be triggered by inhibition of specific molecular targets (e.g. treatment with an anti-angiogenic peptide Angiotensin II (1–7) resulted in higher serum levels of pro-angiogenic factors such as placental derived growth factor [47]). A broad acting pan-integrin inhibitor may show greater clinical activity. Combination of an integrin antagonist with other therapies including conventional chemotherapy could enhance activity.

The trial suffered from a familiar problem seen in previous studies of non-metastatic castration resistant prostate cancer: poor accrual. An ECOG study of chemotherapy compared to ketoconazole (ECOG 1899) closed due to poor accrual. Novel trial designs and endpoints to assess potentially cytostatic therapies in non-metastatic CRPC are urgently needed. PSA based endpoints are likely not suitable to assess activity of cytostatic agents in non-metastatic CRPC. Change in PSA slope was designed into the trial as one possible indicator of drug activity but also relies on PSA. It is also unknown how PSA endpoints relate to clinical objectives in non-metastatic CRPC. The PCCTWG has recommended not relying solely on PSA to stop therapy [32]. In a phase II trial in metastatic CRPC, this approach demonstrated evidence of modest activity for single agent Cilengitide[46, 48]. Several investigators have pointed out the drawbacks in utilizing conventional endpoints in trials of targeted agents and have recommended time to event or progression free survival at a particular timepoint as more suitable[32, 49, 50]. A placebo controlled randomized controlled trial with a clinical end point (e.g. metastasis free survival) may be a more optimal trial design to investigate biological agents in non-metastatic CRPC. The low clinical event rate in the context of non-metastatic CRPC presents a problem in utilizing such an approach as well [1].

There was no MTD identified in the phase I trials of Cilengitide. It is unclear if higher doses of Cilengitide would exhibit increased activity in non-metastatic CRPC. In our trial with this agent in metastatic CRPC, there was a modest increase in TTP between the 500 mg and 2000 mg/dose arms which is the dose we used in the current trial [46].

Cilengitide was well tolerated but did not elicit PSA responses in this trial of non-metastatic CRPC patients. CTCs are of questionable utility in non-metastatic prostate cancer.

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Original Article

Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy

A Phase 2 Study of the Department of Defense Prostate Cancer Clinical Trials Consortium

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BACKGROUND: Mitoxantrone plus prednisone and ixabepilone each have modest activity as monotherapy for second-line chemotherapy in patients with docetaxel-refractory castration-resistant prostate cancer. Clinical noncross-resistance was previously observed. Phase 1 testing determined the maximum tolerated dose and dose-limiting toxicities with the combination regimen; a phase 2 study was conducted to evaluate the activity of the combination. **METHODS:** Patients with metastatic progressive castration-resistant prostate cancer during or after 3 or more cycles of taxane-based chemotherapy enrolled in a phase 2 multicenter study of ixabepilone 35 mg/m^2 and mitoxantrone 12 mg/m^2 administered on Day 1 every 21 days with pegfilgrastim support, along with prednisone 5 mg twice daily. Patients were evaluated for disease response and toxicity. **RESULTS:** Results are reported for the 56 evaluable patients. Twenty-five (45%; 95% confidence interval [CI], 31%-59%) experienced confirmed ≥50% prostate-specific antigen (PSA) declines, 33 (59%; 95% CI, 45%-72%) experienced confirmed ≥30% PSA declines, and 8 of 36 patients (22%; 95% CI, 10%-39%) with measurable disease experienced objective responses. Median time to PSA or objective progression was 4.4 months (95% CI, 3.5-5.6), and median progression-free survival was also 4.4 months (95% CI, 3.0-6.0). Median overall survival was 12.5 months (95% CI, 10.2-15.9). Thirty-two percent of patients experienced grade 3 of 4 neutropenia, and 11% experienced grade 3 or higher neutropenic infections, including 1 treatment-related death. Grade 2 and 3 neuropathy occurred in 11% and 12.5% of patients, respectively. **CONCLUSIONS:** These results suggest that the combination of ixabepilone and mitoxantrone is both feasible and active in castration-resistant prostate cancer and requires dosing with pegfilgrastim. ***Cancer* 2011;00:000–000.** *© 2010 American Cancer Society.*

KEYWORDS: prostate cancer, chemotherapy, metastatic, mitoxantrone, ixabepilone, docetaxel.

Mortality in prostate cancer is primarily related to the development of metastatic castration-resistant disease, and options after docetaxel, the first-line standard of care, remain limited.[1] Recent data have established cabazitaxel as the standard second-line therapy.[2] Mitoxantrone with prednisone, which has been demonstrated to improve quality of life as front-line therapy, has been used extensively, with 50% PSA declines reported in 20% of patients previously treated with docetaxel.[3-5] Ixabepilone, an epothilone analog, has similarly been demonstrated to have a 17% response rate in this setting. Of interest, objective responses to mitoxantrone/prednisone after second-line ixabepilone and conversely to ixabepilone after second-line mitoxantrone/prednisone were observed during a randomized phase 2 study, suggesting there is noncross-resistance with the 2 regimens.

On the basis of the nonoverlapping toxicity of these regimens and their apparent noncross-resistance, a phase 1 study combining these agents was undertaken in patients previously treated with docetaxel.[6] The combination was well

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tolerated. Although hematologic toxicity required treatment with pegfilgrastim, other toxicity, including neurotoxicity, was modest. The regimen recommended for phase 2 testing was mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2, given with prednisone 5 mg twice daily, along with pegfilgrastim 6 mg on Day 2. Responses, as defined by a $\geq$50% PSA decline, were observed in 31% of patients, with objective responses in 2 of 36 patients in the phase 1 study. When limited to the 21 patients treated with 12 mg/m^2 of mitoxantrone plus ixabepilone at a dose of 30 mg/m^2 or higher, 43% of patients experienced prostate-specific antigen (PSA) declines of $\geq$50% (95% confidence interval [CI], 22% to 66%). When compared with the response proportions reported for monotherapy with either ixabepilone or mitoxantrone of approximately 20%, these results suggested at least additive effects of the 2 agents and were sufficiently promising to warrant a phase 2 study to determine the activity of this novel regimen.

MATERIALS AND METHODS

Study Design

This study was a multicenter, single-arm, phase 2 study of ixabepilone and mitoxantrone with prednisone in castration-resistant prostate cancer patients who developed progressive disease during or after docetaxel-based chemotherapy. This study was undertaken in the Department of Defense Prostate Cancer Clinical Trials Consortium, with accrual occurring at 6 academic centers. The primary endpoint of the study was the proportion of patients achieving $\geq$50% PSA declines. Secondary endpoints included overall safety, the frequency of objective responses, time to progression, progression-free survival, and overall survival. This study was approved by the Clinical Trial Evaluation Program of the National Cancer Institute, the Prostate Cancer Clinical Trials Consortium Review Committee, and the local institutional review boards of participating institutions. All patients provided written informed consent.

Eligibility

Patients were required to have histologically confirmed prostate cancer with metastatic spread and progressive disease despite castrate testosterone levels. Patients were required to have received at least 3 cycles of taxane-based chemotherapy, and only 1 prior chemotherapy regimen was permitted. For patients with measurable disease, progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), and for patients without measurable disease, a PSA of $\geq$2 ng/mL and a bone scan consistent with metastasis were required. Patients without measurable disease were required to have either PSA progression or a bone scan demonstrating 1 or more new metastatic lesions. PSA progression was defined according to PSA Working Group 1 criteria.[7] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and $\leq$grade 1 peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0). Patients who had not undergone prior orchiectomy were required to remain on a luteinizing hormone-releasing hormone agonist. Other hormonal therapy, with the exception of prednisone 5 mg twice daily, as given with docetaxel, was not allowed within 4 weeks of study entry. Docetaxel was not allowed within 4 weeks of enrollment. No prior mitoxantrone or ixabepilone was allowed. Radiation or radiopharmaceutical therapy must have been completed at least 4 and 8 weeks, respectively, before enrollment. Cardiac ejection fraction was required to be above the lower limit of normal for the institution. Patients with clinically significant cardiovascular disease, including New York Heart Association class III or IV heart failure, active angina, or a history of myocardial infarction within 6 months, were excluded. Laboratory requirements included testosterone $<$50 ng/dL; creatinine $\leq 1.5 \times$ upper limit of normal (ULN) or calculated creatinine clearance $\geq$40 mL/min; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $<2.5 \times$ ULN; granulocytes $\geq$2000/mm^3; platelets $\geq$100,000/mm^3; and total bilirubin $\leq 1.5 \times$ ULN. Because ixabepilone is a CYP3A4 substrate, concurrent use of moderate to strong CYP3A4 inhibitors was prohibited.

Study Therapy

Patients were treated on day 1 of 21-day cycles. Premedication with oral H1- and H2-blockers was administered 1 hour before treatment to prevent hypersensitivity reactions. Patients received mitoxantrone 12 mg/m^2 intravenously over 30 minutes. Ixabepilone 35 mg/m^2 was subsequently administered as a continuous infusion over 3 hours. Patients were monitored for hypersensitivity reactions for 1 hour. If grade 2 to 4 hypersensitivity reactions developed despite antihistamine premedication, corticosteroid premedication was used for subsequent cycles. Prednisone was administered 5 mg twice daily continuously. Pegfilgrastim 6 mg was administered subcutaneously on Day 2. Patients were treated until disease

progression, unacceptable toxicity, or patient preference to discontinue therapy.

Assessment for Response and Toxicity

Patients were assessed with chest x-ray or chest computed tomography (CT), CT of the abdomen and pelvis, and bone scan every 3 cycles. PSA, complete blood count with differential and platelets, electrolytes, blood urea nitrogen, creatinine, magnesium, lactate dehydrogenase, albumin, AST, ALT, total bilirubin, and alkaline phosphatase were obtained every cycle. Physical examination and assessment of performance status were undertaken each cycle. Echocardiogram or MUGA (Multi Gated Acquisition) Scan was performed at baseline, every 3 cycles, and as clinically indicated.

Objective response was defined by RECIST, and both 50% and 30% PSA declines were determined, with a repeat PSA required 3 weeks later for confirmation.[7,8] Disease progression was defined as new metastases outside of the bone, $\geq$1 new bone lesions confirmed on repeat imaging, a need for radiation while on therapy, unequivocal progression of nontarget lesions, progression by RECIST, or PSA progression. PSA progression was defined according to PSA Working Group 1 criteria, with a PSA increase of 25% above the nadir value, occurring at least 9 weeks (3 cycles) after initiating the study.

Toxicity was monitored by history, physical examination, and laboratory assessment before each cycle. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria version 3.0. For grade 3 or higher toxicities, both ixabepilone and mitoxantrone were held until resolution to $\leq$grade 1, then reinstituted at 5 mg/m^2 less of ixabepilone and 2 mg/m^2 less of mitoxantrone. The same process was required for recurrent toxicities, with a third recurrence resulting in removal from study therapy. For corticosteroid toxicity, prednisone doses could be modified without removing a patient from protocol therapy. For neurotoxicity secondary to ixabepilone, therapy was held for grade 2 or 3 toxicity but otherwise managed as above. Alopecia, lymphopenia, anemia, and toxicities related to androgen deprivation were excluded as dose-limiting or modifying criteria.

Statistical Considerations

The primary endpoint of this study was the proportion of patients responding to treatment defined as observing a PSA decline of $\geq$50% (PSA response) based on PSA Working Group 1 criteria. Treatment of 58 patients allowed for the detection of a PSA response proportion of 35%, compared with a null hypothesis of 20% with a power of 0.90 and a level of significance of 0.10. Simon's MiniMax 2-stage design was used for accrual, to allow for an interim analysis for efficacy after the first 33 patients had been accrued and had been followed for 3 cycles of treatment. Had 6 or fewer of the first 33 patients enrolled demonstrated a PSA decline of $\geq$50%, accrual would have been terminated, resulting in a probability of early termination if the null hypothesis were true of 50%. Objective responses were evaluated according to RECIST for patients with measurable disease. Descriptive statistics were calculated to characterize the patient cohort, baseline disease parameters, outcome, and toxicity. The time to progression, progression-free survival, and overall survival were measured from the start of protocol therapy and evaluated using the Kaplan-Meier product limit method.

RESULTS

Patient Characteristics

Between November 2007 and March 2009, 58 patients were enrolled at 6 member institutions of the Department of Defense Prostate Cancer Clinical Trials Consortium. Two patients were ineligible: 1 because of pre-existing spinal cord compression and 1 because of a secondary diagnosis of colon cancer diagnosed after 2 cycles of therapy; therefore, 56 evaluable patients were included in these analyses. Four patients did not complete the minimum 3 cycles of therapy defined by the protocol to be necessary for response assessment; 2 discontinued for progressive disease and 2 withdrew because of concerns over rising PSA. These 4 patients are included in both efficacy and toxicity analyses. Patient characteristics are summarized in Table 1. The median age of patients at the start of protocol therapy was 66.7 years. Sixty-nine percent of patients had a Gleason score of 8 to 10. Sixty-six percent had an ECOG performance status of 1 to 2, and 34% had an ECOG performance status of 0. The median PSA was 171.2 (range, 2.79-3717.1), and the median alkaline phosphatase was 134 (range, 42-1094). All patients had received prior docetaxel therapy once every 3 weeks. The median number of prior chemotherapy cycles was 8 (range, 3-33). The median prior treatment duration was 6.4 months (range, 2.2-29.1), and the median time between discontinuation of docetaxel and initiation of study therapy was 53 days (range, 5-413). Fifty percent of patients (28 of 56) had experienced a PSA response to prior taxane-based therapy by PSA Working Group 1

Table 1. Patient Characteristics (N=56)

Median age at entry (range)	66.7 (47-83)
ECOG PS at protocol entry, patients (%)	
0	19 (34)
1-2	37 (66)
Gleason score at diagnosis (n=54), patients (%)	
4-6	3 (5.5)
7	14 (26)
8-10	37 (68.5)
Median PSA, ng/mL (range)	171.2 (2.79-3717.1)
Baseline laboratory results at protocol entry	
Median LDH, IU/L (range)	290 (123-2333)
Median alkaline phosphatase, U/L (range)	134 (42-1094)
Median hemoglobin, g/dL (range)	11.7 (9.3-14.1)
Prior chemotherapy: best response, patients (%)	
PSA response/partial response	28 (50)
Stable disease for patients with objective disease	18 (32)
Progressive disease	10 (18)
Prior 3-week chemotherapy cycles, median No. (range)	8 (3-33)
Median duration, mo (range)	6.4 (2.2-29.1)
Median duration from end of taxane, d (range)	53 (5-413)
Study treatment	
Cycles received, median No. (range)	5+ (1-13)
Still on treatment, patients	1[a]

ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
[a] Duration 10.4 months.

Table 2. Response Data

Response	No.	%
≥30% PSA decline	33	59
≥30% PSA decline by 12 weeks	31	55
≥50% PSA decline	25	45
≥50% PSA decline by 12 weeks	17	30
Objective responses	8/36	22

PSA indicates prostate-specific antigen.

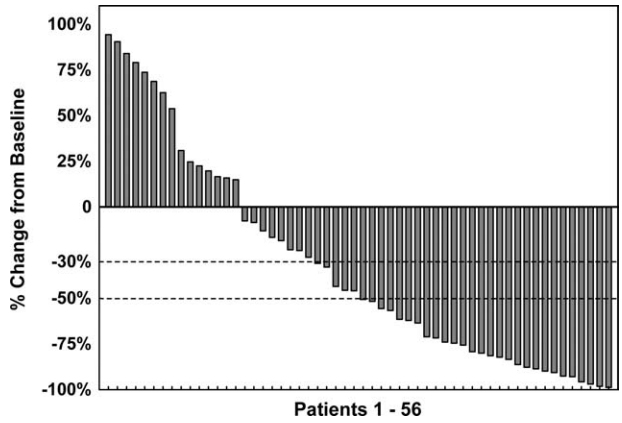

Figure 1. Maximum percentage change in prostate-specific antigen is shown.

criteria, whereas half of the enrolled patients never had a PSA response to docetaxel therapy. Fifty-nine percent of patients had subsequently progressed on docetaxel therapy by PSA criteria alone, 30% had radiographic progression, 9% stopped docetaxel therapy for toxicity, and 2% stopped with stable disease after completing a planned course of therapy. Thus, 89% of patients had developed docetaxel-resistant castration-resistant prostate cancer before enrolling on this trial. Twenty-five percent (14 patients) of patients received therapy after docetaxel but before beginning this study, including ketoconazole (n = 5), sunitinib (n = 3), bicalutamide (n = 2), palliative radiotherapy (N = 2), PSMA ADT (an antibody against prostate specific membrane antigen), and GVAX (a vaccine consisting of prostate cancer cells modified to secrete granulocyte-macrophage colony-stimulating factor), 1 each.

Clinical efficacy to ixabepilone and mitoxantrone with prednisone chemotherapy is reported for all 56 eligible patients (Table 2). Overall, 25 (45%) patients experienced confirmed PSA declines of ≥50% (Fig. 1; 95% CI, 31%-59%), and 33 (59%) had confirmed PSA declines of ≥30% (95% CI, 45%-72%). After 12 weeks of protocol therapy, 30% of the patients achieved PSA declines of at least 50%, indicating that the study null hypothesis of 20% can be rejected (1-sided binomial exact test: $P = .04$). Partial objective RECIST-defined responses were observed in 8 patients of 36 with measurable disease (22%; 95% CI, 10%-39%).

With a median follow-up of 9.9 months (range, 3.1-19.4) from the start of protocol therapy, the median time to progression was 4.4 months (95% CI, 3.5-5.6). The median PSA or objective progression-free survival was also 4.4 months (Fig. 2; 95% CI, 3.0-6.0), and the median overall survival was 12.5 months (Fig. 3; 95% CI, 10.2-15.9).

Patients with a prior response to docetaxel therapy were as likely to respond to ixabepilone and mitoxantrone with prednisone second-line therapy as patients with no prior response to docetaxel. Of the 28 patients who had a ≥50% PSA decline with docetaxel-based therapy, 39% had a ≥50% PSA decline with ixabepilone and mitoxantrone with prednisone. Of the 10 patients whose best

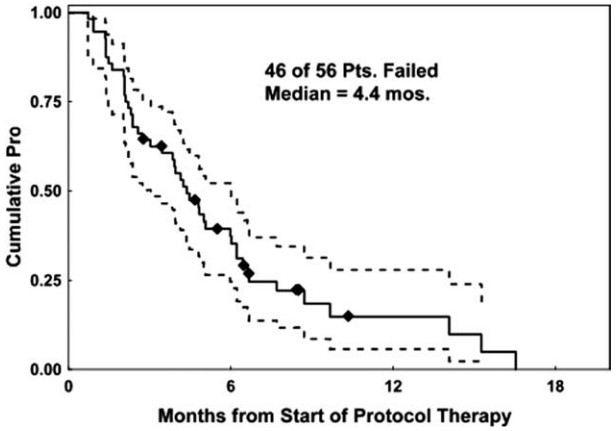

Figure 2. Progression-free survival with ixabepilone and mitoxantrone with prednisone is shown. Pro indicates progression; Pts., patients.

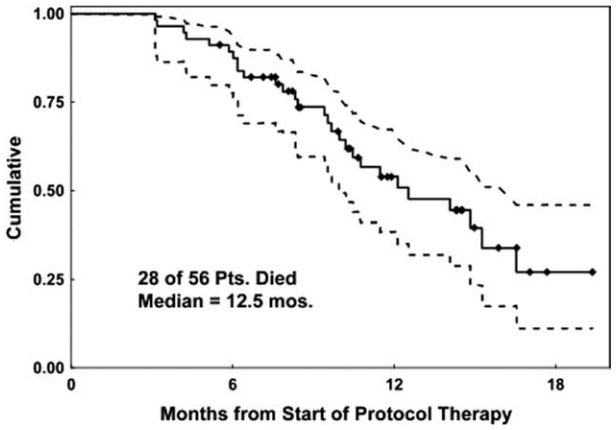

Figure 3. Overall survival with ixabepilone and mitoxantrone with prednisone is shown.

response to docetaxel-based therapy was progressive disease, 40% had a $\geq$50% PSA response to ixabepilone and mitoxantrone with prednisone ($P = .71$).

Toxicity

Toxicity data are reported for all 56 eligible patients and are summarized in Table 3. Thirty-two percent of patients experienced grade 3 or 4 neutropenia. Eleven percent of patients had neutropenia associated with infection. Five grade 3 infections occurred in 5 patients (2 pulmonary, 1 skin, 1 *Clostridium difficile* colitis, 1 septic arthritis of the elbow), and 1 grade 4 bacteremia occurred. One treatment-associated death occurred in the 1 patient on study on verapamil, a moderate CYP3A4 inhibitor. This patient

Table 3. Toxicity Related to Study Therapy

Adverse Event	Grade 3	Grade 4	Grade 5
Hematologic			
Leukopenia	9	11	
Lymphopenia	17	3	
Neutropenia	6	10	
Anemia	3	1	
Thrombocytopenia	7	3	
Nonhematologic			
Allergic reaction	1		
AST/ALT increased	1		
Dyspnea	2		
Fatigue	5		
Hyperbilirubinemia	1		
Hypoalbuminemia	1		
Infection	5[a]	1[a]	1[b]
Hypocalcemia	1		
Hypophosphatemia	1		
Mucositis	1		
Nausea/vomiting	1		
Neuropathy	7		
Vasovagal episode		1	

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Sites of infection: skin (cellulitis), blood (methicillin-resistant *Staphylococcus aureus*, grade 4), pneumonia (2), colon (*Clostridium difficile* colitis), elbow (septic arthritis). All but septic arthritis associated with neutropenia. The *C. difficile* infection occurred in a patient with pneumonia treated with antibiotics.
[b] There was 1 treatment-related death in a patient with urosepsis and neutropenia who was on verapamil.

experienced urosepsis in association with neutropenia. Grade 3 or higher thrombocytopenia and anemia were uncommon (18% and 7%, respectively). Cardiovascular toxicity included 1 grade 4 cardiac infarct, 1 grade 3 atrial fibrillation, and 1 grade 2 decrease in ejection fraction. Grade 2 and 3 sensory neuropathy was observed in 6 and 7 patients (11% and 13%), respectively. Other toxicities of note included grade 2 fatigue in 13 patients and grade 3 fatigue in 5 patients.

Treatment Administered

Patients were removed from study therapy primarily for progressive disease. Twenty-seven and 9 patients (48% and 16%) discontinued protocol treatment because of PSA and objective progression, respectively, and 4 (7%) others had both PSA and objective disease progression. Ten (18%) patients discontinued therapy for toxicity after a median of 7 cycles (range, 1-13). Two (4%) patients discontinued after completing 12 cycles, and 3 (5%) patients withdrew, 2 because of concerns over rising PSA, and 1 because of a combination of toxicity and concerns over rising PSA. One (2%) patient remains on therapy 10.6 months from the start of protocol therapy having received 8 cycles of therapy to date.

DISCUSSION

After progression on docetaxel-based chemotherapy, chemotherapy options for patients with metastatic castration-resistant prostate cancer remain poor. Recently reported data suggest that cabazitaxel may represent an important therapeutic option for patients with progressive disease after docetaxel.[2] Mitoxantrone with prednisone is often used as second-line therapy but is associated with a PSA response rate of only 20%.[5] Ixabepilone also has a disappointing PSA response rate of 17% after docetaxel. The objective response rates associated with ixabepilone monotherapy and mitoxantrone with prednisone after docetaxel are also low at 4% and 10%, respectively. On the basis of results from a randomized phase 2 study suggesting that ixabepilone and mitoxantrone with prednisone have noncross-resistance and a phase 1 trial of the ixabepilone and mitoxantrone with prednisone combination demonstrating surprisingly high activity, the present phase 2 trial was undertaken.[5]

The ixabepilone and mitoxantrone with prednisone regimen was found to have significant activity, with a PSA response proportion of 45%, and an equally promising objective response proportion of 22%. The overall survival in this group of patients was 12.5 months. Although direct comparisons are not possible across studies, and differences in patient populations may account for results observed, it is notable that the overall survival was 10.4 months on the ixabepilone arm (with mitoxantrone on progression) and 9.8 months on the mitoxantrone arm (with ixabepilone on progression) in the randomized phase 2 study of ixabepilone or mitoxantrone after docetaxel. The time to progression of 4.4 months also appears favorable in comparison to the 2.3-month time to progression on mitoxantrone monotherapy in the randomized phase 2 study.

Data from a randomized phase 3 study comparing cabazitaxel to mitoxantrone with prednisone in patients who had progressed after docetaxel-based therapy indicated that cabazitaxel was associated with a PSA response proportion of 39%, in comparison to 18% on the mitoxantrone/prednisone arm. Although these results cannot be directly compared with the results of the current study of ixabepilone with mitoxantrone and prednisone, the response proportion of 45% in the current study suggests further study may be warranted.

Of interest, response to ixabepilone and mitoxantrone with prednisone does not appear to be dependent on prior response to docetaxel. Although definitive conclusions cannot be drawn given the small numbers of patients, these data suggest that there is no significant cross-resistance between docetaxel and ixabepilone/mitoxantrone with prednisone, and that ixabepilone and mitoxantrone with prednisone therapy may be useful in patients with progressive disease after docetaxel, regardless of docetaxel sensitivity.

The combination of these 2 agents did not appear to result in a dramatic increase in toxicity. Although comparison across studies is fraught with difficulty, toxicity with the study regimen appears to be similar to that associated with mitoxantrone/prednisone use in the second-line alone. In the randomized phase 2 study of mitoxantrone/prednisone and ixabepilone monotherapy, 10% of the 41 patients on the mitoxantrone/prednisone second-line arm experienced febrile neutropenia, and 9% of the 56 patients on this study of the combination (with pegfilgrastim support) experienced febrile neutropenia. It is important to note, however, that this margin of safety can be achieved with the ixabepilone and mitoxantrone with prednisone regimen at the doses studied only with pegfilgrastim support.

Sixteen percent of patients discontinued therapy for toxicity in this phase 2 study of the combination, a number that appears to be similar to the number of patients discontinuing docetaxel as first-line treatment for toxicity. In the randomized phase 2 study of mitoxantrone or ixabepilone, 10% of the 41 patients on mitoxantrone discontinued therapy for toxicity.[1]

Nonhematologic toxicity was minimal. Despite substantial doses of mitoxantrone (66% of patients received >6 cycles), minimal cardiac toxicity was observed. Similarly, less neuropathy was observed than expected in this taxane-pretreated population, with 11% and 12.5% of patients developing grade 2 and 3 neurotoxicity, respectively. However, these results may reflect patient selection. As with the prior second-line ixabepilone prostate cancer studies, patients with grade 2 or higher neuropathy at baseline after docetaxel were excluded. This may have selected a patient population less likely to experience neuropathy. Nevertheless, neuropathy was comparable to that seen in breast cancer studies[9-13] in which 12% to 20% of patients develop grade 3 neurotoxicity.

One potential weakness of this study is that the eligibility criteria did not require a previous history of progression while receiving docetaxel-based therapy, but rather required disease progression during or after docetaxel therapy, possibly selecting for a more chemotherapy-sensitive population. However, 89% of the patients on study had, in fact, progressed while receiving docetaxel therapy, suggesting that this study enrolled patients with

docetaxel resistance. Furthermore, there did not appear to be a difference in response proportion as a function of prior response to docetaxel, although small numbers limit this analysis.

Another potential criticism of this study is that the primary endpoint, the proportion of patients achieving a $\geq$50% decline in PSA, per PSA Working Group Criteria, is of uncertain clinical significance. However, the PSA Working Group criteria were initially established to be used specifically in this setting, as a screen for the activity of cytotoxic agents in the phase 2 setting.[7] In addition, the objective response proportion, time to progression, and overall survival observed with ixabepilone and mitoxantrone with prednisone therapy all appeared to be favorable compared with that associated with mitoxantrone monotherapy, suggesting that the high proportion of patients with an observed PSA decline may be associated with improved survival outcomes. Definitive evidence of benefit can only be established by evaluating overall survival in a phase 3 study.

In summary, the combination of ixabepilone and mitoxantrone with prednisone appears to have greater activity than either mitoxantrone or ixabepilone alone in the second-line setting for castration-resistant prostate cancer, and suggests at least additive if not synergistic activity in a disease state where improvement in outcome is needed and long overdue. The combination is well tolerated, although some hematologic toxicity is present and dosing with pegfilgrastim is required. The results of this study suggest that it is appropriate to study further the ixabepilone and mitoxantrone with prednisone regimen in patients with docetaxel-resistant castration-resistant prostate cancer.

CONFLICT OF INTEREST DISCLOSURES

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APPENDIX CC

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ORIGINAL ARTICLE

A randomized, phase II study of pazopanib in castrate-sensitive prostate cancer: a University of Chicago Phase II Consortium/Department of Defense Prostate Cancer Clinical Trials Consortium study

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BACKGROUND: Intermittent androgen suppression (IAS) is an increasingly popular treatment option for castrate-sensitive prostate cancer. On the basis of previous data with anti-angiogenic strategies, we hypothesized that pan-inhibition of the vascular endothelial growth factor receptor using pazopanib during the IAS off period would result in prolonged time to PSA failure.

METHODS: Men with biochemically recurrent prostate cancer, whose PSA was $<0.5\,ng\,ml^{-1}$ after 6 months of androgen deprivation therapy were randomized to pazopanib 800 mg daily or observation. The planned primary outcome was time to PSA progression $>4.0\,ng\,ml^{-1}$.

RESULTS: Thirty-seven patients were randomized. Of 18 patients randomized to pazopanib, at the time of study closure, 4 had progressive disease, 1 remained on treatment and 13 (72%) electively disenrolled, the most common reason being patient request due to grade 1/2 toxicity (8 patients). Two additional patients were removed from treatment due to adverse events. Of 19 patients randomized to observation, at the time of study closure, 4 had progressive disease, 7 remained under protocol-defined observation and 8 (42%) had disenrolled, most commonly due to non-compliance with protocol visits (3 patients). Because of high dropout rates in both arms, the study was halted.

CONCLUSIONS: IAS is a treatment approach that may facilitate investigation of novel agents in the hormone-sensitive state. This trial attempted to investigate the role of antiangiogenic therapy in this setting, but encountered several barriers, including toxicities and patient non-compliance, which can make implementation of such a study difficult. Future investigative efforts in this arena should carefully consider drug toxicity and employ a design that maximizes patient convenience to reduce the dropout rate.

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Keywords: intermittent androgen suppression; tyrosine kinase inhibitors; pazopanib randomized consortium trial

Introduction

The importance of androgen deprivation for treatment of prostate cancer has been known since the 1940s.[1,2] Over the past 70 years, many novel and highly effective treatments have been introduced; however, continuous androgen suppression (CAS) currently remains the standard of care for men with hormone-sensitive metastatic disease. Intermittent androgen suppression (IAS)[1] is a concept that advocates alternating periods of treatment with and without androgen suppression. The body of literature which supports its use is growing.[3–T4] Preliminary results of an ongoing multicenter, randomized, controlled phase III trial comparing IAS and CAS in a population of patients with biochemical recurrence following local therapy (NCIC PR7) were recently presented; they demonstrated that IAS was non-inferior to CAS with a mean overall survival of 8.8 years and 9.1 years, respectively (hazard ratio = 1.02, 95% confidence interval = 0.86–1.21; *P*-value for non-inferiority (hazard ratio for IAS vs CAS > 1.25) = 0.009). IAS patients had fewer hot flashes. Quality-of-life data are not yet evaluable.[15]

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Several investigators have proposed ways to increase the 'off' period of IAS, with the hypothesis that this could improve treatment efficacy, and possibly even decrease long-term androgen deprivation therapy (ADT) toxicities. One class of medications under investigation for this purpose are angiogenesis inhibitors.[16–21] Elevated plasma and urine vascular endothelial growth factor (VEGF) levels have been correlated with shortened survival times in men with hormone refractory disease,[22,23] leading to the hypothesis that anti-angiogenesis agents may have a role in prostate cancer treatment. *In vivo* models using Shionogi mice have shown that castration leads to a regression in the size of androgen-dependent tumors that is coupled with a decrease in VEGF expression;[24] however, when tested, anti-angiogenesis agents have not yet demonstrated survival benefits in men with prostate cancer.

Pazopanib is an orally available multi-targeted tyrosine kinase inhibitor with broad activity against VEGF receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α, PDGFRβ, and c-kit among others,[25] and is a standard available therapy for advanced renal cell carcinoma.[26] In this randomized, phase II study, we tested the hypothesis that pazopanib could prolong the 'off' period of IAS.

Materials and methods

Study objectives

The primary objective was to determine if pazopanib was able to increase time to PSA progression (TTPP) following 6 months of androgen blockade in patients with stage D0 prostate cancer. Secondary objectives were to describe progression-free survival and adverse events (AEs) related to pazopanib in this population, as well as to monitor and compare changes in testosterone in the two treatment arms.

Patients and eligibility criteria

Eligible patients had pathologically confirmed prostate cancer, had received definitive local therapy and had evidence of biochemical recurrence, defined as two consecutive rises in PSA above the nadir, following definitive local therapy. Patients with radiologically detectable disease were excluded, which was confirmed with a bone and CT scan if the baseline PSA level was greater than 10 ng ml^{-1}. Prior ADT was disallowed. All patients had an Eastern Cooperative Oncology Group performance status $\leqslant 2$, normal renal and hepatic function as defined by the Common Terminology Criteria for Adverse Events v3.0 (CTCAE 3.0), as well as a urine protein to creatinine ratio of <1.

Patients were excluded if they had uncontrolled hypertension ($>140/90$ mm Hg), New York Heart Association class III or IV heart failure, a history of cerebrovascular accident, myocardial infarction, unstable angina, or coronary artery stenting within 6 months of enrollment, or a history of venous thrombosis within 12 weeks of enrollment. Patients who required treatment with strong CYP450 3A4 inhibitors or inducers were not allowed to participate. Other exclusion criteria included inability to take oral medications and patients with HIV on anti-retroviral therapy.

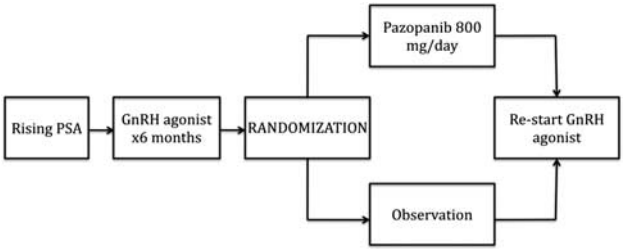


Figure 1 Schema for the randomized, placebo-controlled, phase II study.

Study design

This study employed a multicenter, two-arm, randomized, phase II design. Each center's Institutional Review Board approved the investigational protocol and all subjects provided written informed consent in accordance with the Helsinki Declaration of 1975. The study schema is depicted in Figure 1. Upon verification of eligibility, subjects were enrolled and completed a period of 6 months of androgen blockade with a gonadotropin-releasing hormone agonist without concomitant anti-androgen therapy. At this time, if the subject's PSA was <0.5 ng ml^{-1} and total serum testosterone level was <50 ng ml^{-1}, he was randomized to treatment with pazopanib 800 mg daily or observation.

The primary endpoint was TTPP, which was measured as the time from randomization until the total serum PSA was >4.0 ng ml^{-1}, with non-cancer and non-treatment-related deaths censored. The secondary endpoint was progression-free survival, defined as the time from randomization until the time of PSA progression or death from any cause. Subjects were seen monthly with physical examination, history, PSA and testosterone evaluation. Subjects remained on either pazopanib or active surveillance until they met the TTPP criteria withdrew consent, or were removed by the investigator for adverse events or other reasons.

Subjects were monitored for toxicity on a monthly basis, and adverse events were classified according to the CTCAE v3.0. All patients measured their blood pressure on a twice-daily basis while on trial and maintained a blood pressure diary. Specific guidelines were provided for management of treatment-associated hypertension, transaminitis and proteinuria. All subjects were followed for 12 months after disenrollment from the study for toxicity evaluation.

Statistical analysis

The study was designed to achieve 85% power to detect a difference of 5 versus 9 months in the median TTPP between the two study treatment groups at the one-sided 0.10 significance level, allowing for a 15% rate of non-cancer deaths. This required a sample size of 94 patients, 47 in each arm. The planned statistical analysis included calculating the Kaplan–Meier estimates of the primary endpoint, TTPP, as well as the secondary endpoint of progression free survival, and comparison of TTPP and

progression free survival between the two treatment arms using the log-rank test.

Table 1 Baseline patient characteristics

	Observation (n = *19*)	*Pazopanib* (n = *18*)
Primary Gleason score	3.63 (s.d. 0.50)	3.61 (s.d. 0.70)
Secondary Gleason score	3.63 (s.d. 0.68)	3.61 (s.d. 0.70)
Stage		
⩾T3	66.7% (10/15 pts)	41.7% (5/12 pts)
⩽T2	33.3% (5/15 pts)	58.3% (7/12 pts)
Primary therapy		
Surgery	94.7% (18/19 pts)	72.2% (13/18 pts)
Radiotherapy	5.3% (1/19 pts)	27.8% (5/18 pts)
Pre-ADT treatment PSA ($ng\,ml^{-1}$)	3.29 (s.d. 2.94)	11.09 (s.d. 15.03)
Undergoing salvage radiotherapy %	78.9 (15/19 pts)	52.9 (9/17 pts)

Abbreviations: ADT, androgen deprivation therapy; pts, patients.

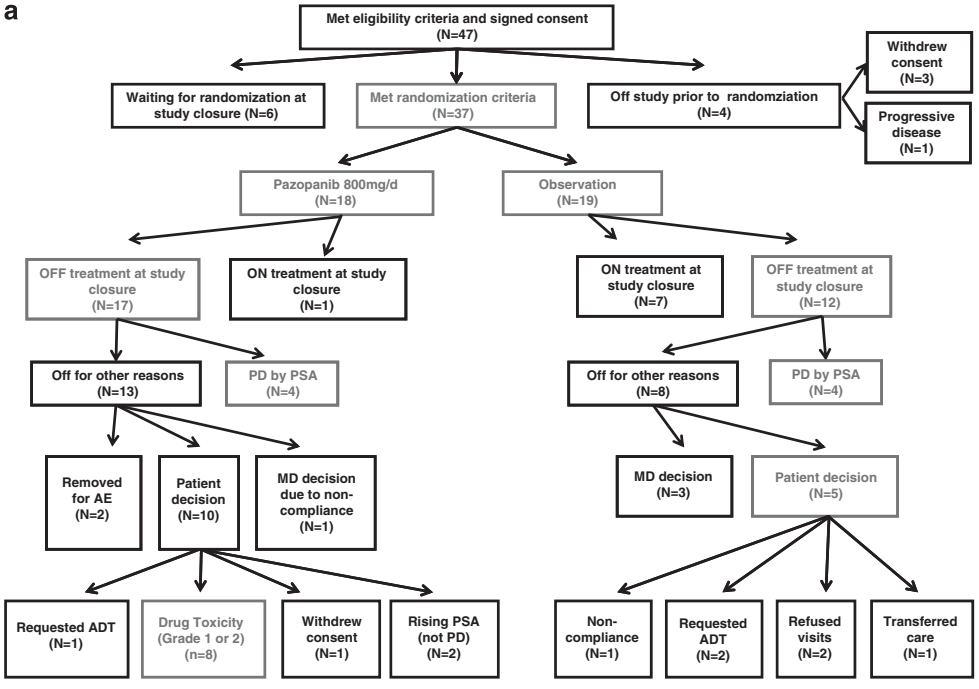
Results

Patient data and treatment outcomes

Baseline patient characteristics are shown in Table 1. There were no statistically significant differences between the treatment arms in any of the relevant categories at the $\alpha = 0.05$ level. Because of high patient dropout, early closure was recommended by the Data Safety and Monitoring Board, as it was no longer possible to validly test the primary hypothesis. At the time that the study was stopped, 37 patients had been randomized, 18 to pazopanib and 19 to observation. We report here the findings from these 37 evaluable patients.

A flowchart outlining the reasons for subject disenrollment is provided in Figure 2a. Seventeen of the 18 patients randomized to the pazopanib arm were off treatment at the time of study closure. Four of the 18 patients (22%) reached the primary endpoint of PSA progression. Thirteen of the 18 patients went off study for other reasons. Two of the 18 (11%) patients were removed for an AE; one patient sustained a pulmonary embolism (Grade 4) and one showed recurrent grade 2 hepatotoxicity, despite dose adjustment. An additional patient was

a



b

	PAZOPANIB	OBSERVATION
Reached study endpoint: PD	22.0% (4/18 pts)	21.0% (4/19 pts)
Off study for other reasons	72.0% (13/18 pts)	42.0% (8/19 pts)
Disenrolled due to drug side effects	44.4% (8/18 pts)	0.0% (0/19 pts)
Disenrolled due to study related visits/rules	16.7% (3/18 pts)	26.3% (5/19 pts)

Figure 2 (**a**) Flowchart of patient accrual and reasons for study discontinuation. (**b**) Patient outcomes including most common reasons for study discontinuation. ADT, androgen deprivation therapy; AE, adverse effects; Pts, patients.

Table 2 Reported adverse events including most commonly occurring toxicities[a]

Event	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*	*Total*
No. of events	67	27	12	1	107
Diarrhea	8	3	2	—	13
Fatigue	6	3	—	—	9
Hypertension	2	2	3	—	7
↑ ALT	3	2	2	—	7
↑ AST	5	1	1	—	7

[a]All adverse events reported here (attribution ⩾3, possibly, probably or definitely related to treatment) were documented in the pazopanib arm.

removed by a study investigator due to non-compliance (undiagnosed pre-existing dementia, unrelated to treatment). Ten patients withdrew consent, including eight patients (44%) due to drug toxicity (Grades 1–2). Of these eight patients, four withdrew in less than 2 months, another three withdrew between 2–6 months, and one patient withdrew after 18 months. One patient requested further treatment with ADT and one patient did not provide a reason for withdrawal of consent.

Of the 19 patients who were randomized to the observation arm, 12 (63%) were off treatment at the time of study closure. Four patients out of 19 (21%) met the primary endpoint of PSA progression. Three patients (16%) were removed by the study investigators, including one for non-compliance. Five patients (26%) withdrew consent, including two patients who requested further treatment with ADT, two patients who refused study-related visits, and one patient who transferred care. Including the one patient removed by study investigators due to non-compliance, five patients (26%) in this treatment arm left the study due to issues surrounding the study protocol. All five of these patients left or were removed from the study within 5 months of randomization. Patient outcomes are summarized in Figure 2b.

Toxicity data

All AEs were classified according to CTCAE 3.0. The number and grade of the AEs recorded during the study period are listed in Table 2. All of these were in patients receiving pazopanib. No AEs designated as possibly, probably or definitely related to the treatment were observed in the observation arm. There were a total of 12 grade 3 AEs in 10 patients: 3 patients with hypertension, 2 patients each with diarrhea and increased ALT, and 1 patient each with increased AST, anorexia, hypophosphatemia, hyponatremia and dizziness. There was one grade 4 event, a pulmonary embolism. The most commonly occurring AEs (Table 2) were diarrhea, hypertension, increased ALT and increased AST, each with a maximum documented grade of 3 and fatigue, with a maximum grade of 2.

Discussion

IAS is an emerging standard of care for biochemically recurrent prostate cancer and has been proposed as a useful clinical model for developing novel agents in castrate-sensitive prostate cancer. Because the re-growth of cancer during the off period is presumably accompanied by angiogenesis,[24] angiogenic inhibitors in general and VEGF pathway inhibitors specifically have been hypothesized to be useful in this setting. We undertook a randomized phase II trial with the VEGFR tyrosine kinase inhibitor pazopanib to test this hypothesis.

Unfortunately and somewhat unexpectedly, the high dropout rate in both arms of this trial made measurement of the primary outcome at the planned power and significance levels infeasible. The most common reason for dropout in the pazopanib arm was drug-related toxicity (across all grades) accounting for 44% of these patients. The toxicity was predominantly grade 1 or 2 by convention. Compared with published data of pazopanib in advanced renal cell carcinoma, the frequency and severity of toxicities noted in this study were similar and yet the dropout rate was substantially higher, 44.4 versus $<6\%$ in the pazopanib arm and 26.3 versus $<3\%$ in the control arm.[26] Studies of other VEGFR inhibitors in patients with castrate-resistant prostate cancer have mostly demonstrated similar toxicities without the same issues of patient drop out. One such phase II study of sunitinib in patients with mCRPC in the post-chemotherapy setting did have significant patient dropout (52.8%).[27] However, an ongoing phase II study, as well as a completed phase II study of sunitinib in patients with castrate-resistant disease did not report the same difficulties with patient dropout, despite a similar toxicity profile.[1,28] Several phase II studies of sorafenib in patients with castrate-resistant disease also did not report high levels of patient dropout.[21,29,30] To our knowledge, however, VEGFR inhibitors have not been studied in the setting of biochemical recurrence, nor has mature data of pazopanib in prostate cancer been presented.

The fact that this trial had higher dropout rates than other studies with pazopanib or other members of this drug class, despite similar toxicity data, suggests a lower tolerance for drug-related AEs in the setting of IAS. Patients on the off period of IAS suffer fewer adverse effects (hot flashes),[15] and these data suggest it is reasonable to conclude that this population of patients has an expectation for lower treatment-related toxicity and thus, has a higher likelihood to dropout of clinical studies due to treatment related adverse events. The currently used CTCAE classification system may be appropriate for reporting severity of toxicity and the danger patients experience on treatment. However, dose adjustment guidelines based on these criteria cannot be uniformly applied across tumor models and across the spectra of health states that exist within tumor models. Simply stated, a patient with hormone-sensitive prostate cancer with no symptomatology has presumably less incentive to endure the same level of toxicity or adhere to a prescribed visit schedule as a patient with advanced renal cell carcinoma appropriate for medical intervention. This conclusion is bolstered by the finding in this study that patients in the observation arm also dropped out at a higher than expected rate, despite recruitment at centers with expertize and experience in accruing to trials with both novel therapeutic agents and intermittent hormonal therapy. The most common reason for patient dropout, occurring in 26% of the patients in this arm of the study, was due to protocol-related visits and procedures.

The experience of patients in this study provides an important lesson. Given the preliminary results of the

National Cancer Institute of Canada PR7 study,[15] it is likely that the usage of IAS as a therapeutic strategy for men with castrate-sensitive prostate cancer will grow. It follows that future clinical trials will continue to investigate new therapies with the goal of lengthening TTPP, thus allowing for longer periods of time-off of ADT during IAS. This study indicates that patients within this population have a low threshold for drug-related toxicity and protocol-related visits and procedures. Future trial design within this therapeutic niche should take these results into consideration.

Conflict of interest

Dr Posadas has received compensation from GlaxoSmithKline as a member of their speaker's bureau. Drs Ward, Karrison, Chatta, Hussain, Shevrin, Szmulewitz, O'Donnell and Stadler have nothing to disclose.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cabozantinib in Patients With Advanced Prostate Cancer: Results of a Phase II Randomized Discontinuation Trial

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ABSTRACT

Purpose
Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with activity against MET and vascular endothelial growth factor receptor 2. We evaluated the activity of cabozantinib in patients with castration-resistant prostate cancer (CRPC) in a phase II randomized discontinuation trial with an expansion cohort.

Patients and Methods
Patients received 100 mg of cabozantinib daily. Those with stable disease per RECIST at 12 weeks were randomly assigned to cabozantinib or placebo. Primary end points were objective response rate at 12 weeks and progression-free survival (PFS) after random assignment.

Results
One hundred seventy-one men with CRPC were enrolled. Random assignment was halted early based on the observed activity of cabozantinib. Seventy-two percent of patients had regression in soft tissue lesions, whereas 68% of evaluable patients had improvement on bone scan, including complete resolution in 12%. The objective response rate at 12 weeks was 5%, with stable disease in 75% of patients. Thirty-one patients with stable disease at week 12 were randomly assigned. Median PFS was 23.9 weeks (95% CI, 10.7 to 62.4 weeks) with cabozantinib and 5.9 weeks (95% CI, 5.4 to 6.6 weeks) with placebo (hazard ratio, 0.12; $P < .001$). Serum total alkaline phosphatase and plasma cross-linked C-terminal telopeptide of type I collagen were reduced by ≥ 50% in 57% of evaluable patients. On retrospective review, bone pain improved in 67% of evaluable patients, with a decrease in narcotic use in 56%. The most common grade 3 adverse events were fatigue (16%), hypertension (12%), and hand-foot syndrome (8%).

Conclusion
Cabozantinib has clinical activity in men with CRPC, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans, and reductions in bone turnover markers, pain, and narcotic use.

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INTRODUCTION

The receptor tyrosine kinase MET, its ligand hepatocyte growth factor (HGF), and the vascular endothelial growth factor (VEGF) signaling pathway seem to play critical roles in the development and progression of castration-resistant prostate cancer (CPRC). Prominent expression of MET has been observed in primary and metastatic prostate carcinomas,[1,2] with evidence for higher levels of expression in bone metastases compared with lymph node metastases or primary tumors.[3,4] Elevated levels of either HGF or VEGF in plasma or urine are associated with shorter overall survival in men with prostate cancer,[5-7] and expression of MET is higher in tumor samples from patients with CRPC compared with tumor samples from patients who have not yet undergone androgen-deprivation therapy.[8] HGF and MET expression are increased in androgen-sensitive tumor cells after withdrawal of androgen and in castration-resistant xenograft models,[1,9,10] suggesting that upregulation of MET signaling is associated with the emergence of resistance to androgen suppression.

Both HGF and MET are expressed by osteoblasts and osteoclasts in vitro and mediate cellular responses such as proliferation, migration, and differentiation.[11,12] Secretion of HGF by osteoblasts is a key factor in osteoblast/osteoclast coupling[12] and the development of bone metastases by tumor cells

that express MET.[13] Osteoblasts and osteoclasts also express VEGF and its receptors, and VEGF signaling is involved in potential autocrine and/or paracrine feedback mechanisms regulating cellular functions.[14,15] VEGF may also activate the MET pathway in tumor cells by binding to neuropilin-1, which is frequently upregulated in prostate cancer and activates MET in a coreceptor complex.[3]

Cabozantinib (XL184) is an orally bioavailable tyrosine kinase inhibitor with potent activity against MET and VEGF receptor 2 (VEGFR2). In vivo, cabozantinib suppresses MET and VEGFR2 signaling, rapidly inducing apoptosis of endothelial cells and tumor cells, resulting in tumor regression in a variety of xenograft models.[16,17] In a xenograft model of CRPC in bone, cabozantinib blocks the progression of osteolytic and osteoblastic lesions.[18] In phase I clinical studies, treatment with cabozantinib resulted in tumor regression in multiple cancer types.[19] On the basis of the broad activity, a phase II randomized discontinuation trial was conducted in nine selected tumor types including CRPC (ClinicalTrials.gov identifier: NCT00940225).[20] This report describes the results of this trial in the subset of patients with CRPC.

PATIENTS AND METHODS

Patients

Eligible patients had CRPC with measurable disease by RECIST (version 1.0)[21] with progressive disease at screening, Eastern Cooperative Oncology Group performance status of 0 or 1, absolute neutrophil count $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, hemoglobin $\geq$ 9 g/dL, total bilirubin $\leq$ 1.5$\times$ the upper limit of normal (ULN), serum albumin more than 2.8 g/dL, AST and ALT $\leq$ 2.5$\times$ the ULN ($\leq$ 5$\times$ the ULN with liver metastases), and serum creatinine $\leq$ 1.5$\times$ the ULN or calculated creatinine clearance $\geq$ 60 mL/min. Patients had $\leq$ one prior standard chemotherapy regimen completed at least 4 weeks before study entry, and those on combined androgen blockade underwent antiandrogen withdrawal while luteinizing hormone–releasing hormone agonists were maintained. Patients with an increasing prostate-specific antigen (PSA) as their only evidence of progressive disease, brain metastases, radiation therapy within 2 weeks, or clinically significant intercurrent illness were excluded. The study protocol and informed consent documents were reviewed and approved by the institutional review boards of the participating institutions, and informed consent was obtained from all patients before any study-specified procedures.

Study Design

The primary objective of this trial was to evaluate the efficacy of cabozantinib in multiple solid tumors including CRPC. Secondary objectives included assessing the safety and tolerability of the agent and potential pharmacodynamic effects. The study was designed as a randomized discontinuation trial as described by Ratain et al.[22] Key features of this design are the ability to evaluate multiple tumor types simultaneously while minimizing exposure to placebo in tumors with objective regression, yet allowing for randomized evaluation where the activity is to prolong progression without regression. All patients received open-label treatment with cabozantinib during a 12-week lead-in stage (Appendix Fig A1, online only). Patients with stable disease at 12 weeks were randomly assigned to cabozantinib or placebo. Randomly assigned patients were observed until progression, at which point treatment assignment was unblinded. Patients were taken off study if they were receiving cabozantinib or were allowed to restart cabozantinib if on placebo. Patients restarted on cabozantinib after first progression on placebo were observed until subsequent progression.

Study Drug Administration

Patients received an initial daily dose of cabozantinib 100 mg. Dosing was interrupted for intolerable grade 2 toxicity, $\geq$ grade 3 nonhematologic toxicity that was not easily managed, urine protein/creatinine ratio more than 2, persistent hypertension $\geq$ grade 2, or any grade 4 hematologic toxicity. If dosing was interrupted, therapy was restarted if the toxicity had resolved to $\leq$ grade 1 or baseline levels within 3 weeks. If the adverse event was unrelated to study therapy, treatment was resumed with no change in dose. If the adverse event was related to study treatment, dosing resumed at a reduced dose of 60 mg per day, with subsequent reductions to 39.4 mg per day and 19.7 mg per day. Interruption in dosing for more than 3 weeks required discontinuation of the patient from study therapy.

Study Assessments

Patients were evaluated every 3 weeks for safety and every 6 weeks for efficacy. Efficacy assessments included radiographic soft tissue and bone imaging. Progression-defining events for progression-free survival (PFS) analysis were evidence of radiographic tumor progression (RECIST) or death. Response was assessed by the treating investigator. Bone scan changes were independently assessed by a single reader at a radiology facility (MedQIA, Los Angeles, CA) without knowledge of the clinical or biochemical status of the patients. Bone scan effects were categorized as complete resolution, partial resolution, stable disease, or progressive disease (Appendix, online only).

Other clinical assessments included medical and cancer history, physical examination, vital signs and body weight, electrocardiography, Eastern Cooperative Oncology Group performance status, safety laboratories (serum chemistry, hematology, coagulation, and urinalysis), concomitant medications, adverse events, and information on subsequent anticancer treatment. Assessments for analyses of exploratory end points included serum PSA and bone markers (plasma cross-linked C-terminal telopeptide of type I collagen [CTx]

Table 1. Baseline Demographics and Clinical Characteristics of the Patients

Demographic or Clinical Characteristic	No. of Patients	%
Age, years		
Median	68	
Range	47-88	
$\geq$ 75	39	23
ECOG performance status		
0	88	52
1	82	48
Time since diagnosis, years		
Median	6.9	
Range	0.6-22.2	
Measurable disease	170	99
Disease location		
Lymph nodes	136	80
Visceral, lung	42	25
Visceral, liver	25	15
Bone	149	87
$\geq$ 2 disease sites	139	81
Prior treatment		
Chemotherapy	79	46
Docetaxel	74	43
Abiraterone	8	5
Enzalutamide	9	5
Bisphosphonate use*	66	39
Denosumab use*	1	1
Baseline bone pain†	92	54
Narcotics use for bone pain	71	42
Median laboratory values		
Serum prostate-specific antigen, ng/mL	65	
Total alkaline phosphatase, U/L	112	
Hemoglobin, g/dL	12.4	
Lactate dehydrogenase, U/L	232	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Prior or concurrent use of bisphosphonate or denosumab at baseline.
†Investigator survey of patients with bone metastasis at baseline.

and serum total alkaline phosphatase [tALP]). Pain and narcotic analgesic use was retrospectively obtained by survey of medical records.

Statistical Considerations

The study used an adaptive design in which it was assumed that a stable disease rate of at least 35% in a cohort would be of interest and warrant further exploration. Enrollment onto a cohort could be halted by the Study Oversight Committee (SOC) if an insufficient number of patients had disease stabilization as a result of higher than expected rates of either progressive disease or response by RECIST during the lead-in stage. Multiple cohorts were to be closed such that only two cohorts would fully accrue the random assignment stage. Up to 200 patients could be enrolled onto a tumor type cohort to randomly assign 70 patients and achieve 52 events after random assignment. This design had an 80% power to detect a hazard ratio of 0.5 for PFS after random assignment. Random assignment was 1:1 using a permuted-block design with each tumor type cohort without other stratification factors. Each tumor type was analyzed separately, and no adjustments were made for multiple comparisons. The Kaplan-Meier method was used to estimate medians for the analysis of PFS from random assignment, and the log-rank test was used for inference testing. Hazard ratios were estimated using the Cox proportional hazards model. The piecewise estimation method, as described by Ratain et al,[22] was used to analyze overall PFS from the date of first dose, including the lead-in stage. All treated patients contributed to the PFS estimate through the first 12 weeks. After week 12, the PFS was estimated as a weighted average with the weights corresponded to the fraction of patients continuing on open-label treatment and the proportion of patients randomly assigned at week 12 (including placebo).

RESULTS

Patients and Treatment

From October 2009 through February 2011, a total of 171 patients with metastatic CRPC were enrolled in the United States, Belgium, Israel, and Taiwan. Baseline demographics and clinical characteristics are listed in Table 1. Bone metastases were present in 149 patients (87%). Forty-six percent of patients had prior chemotherapy, 94% with docetaxel-based therapy, and 39% of patients had prior and ongoing bisphosphonate treatment. The SOC recommended suspension of random assignment after enrollment of 122 patients because of unexpected changes on bone scan and decrease in pain observed during the lead-in stage. At the time random assignment was suspended, 31 patients had been randomly assigned to either receive cabozantinib or placebo, and 57 patients continued open-label treatment. Numerous potential patients had been approached or consented to the protocol, and an additional 49 eligible patients were enrolled before closure of the cohort. Of these 49 patients, 28 remained on treatment for more than 12 weeks. Overall, treatment was discontinued during the lead-in stage (≤ week 12) in 32% of patients (55 of 171 patients). In 21 patients, this was a result of an adverse event. The median duration of cabozantinib treatment excluding patients randomly assigned to placebo was 4.2 months (range, 0.5 to 17.2 months). Treatment status for all 171 patients is summarized in Figure 1.

Response

Of the 171 men enrolled, 170 had measurable disease at baseline, and 154 were evaluable for response assessment per RECIST with at least one postbaseline radiographic assessment. Nine patients (5%) had a confirmed partial response within the first 12 weeks, 127 (75%) had stable disease, and 18 (11%) had disease progression (Table 2). In addition, four patients with stable disease at week 12 had a confirmed partial response after the lead-in stage. Of 154 patients evaluable for best change in measurable disease,

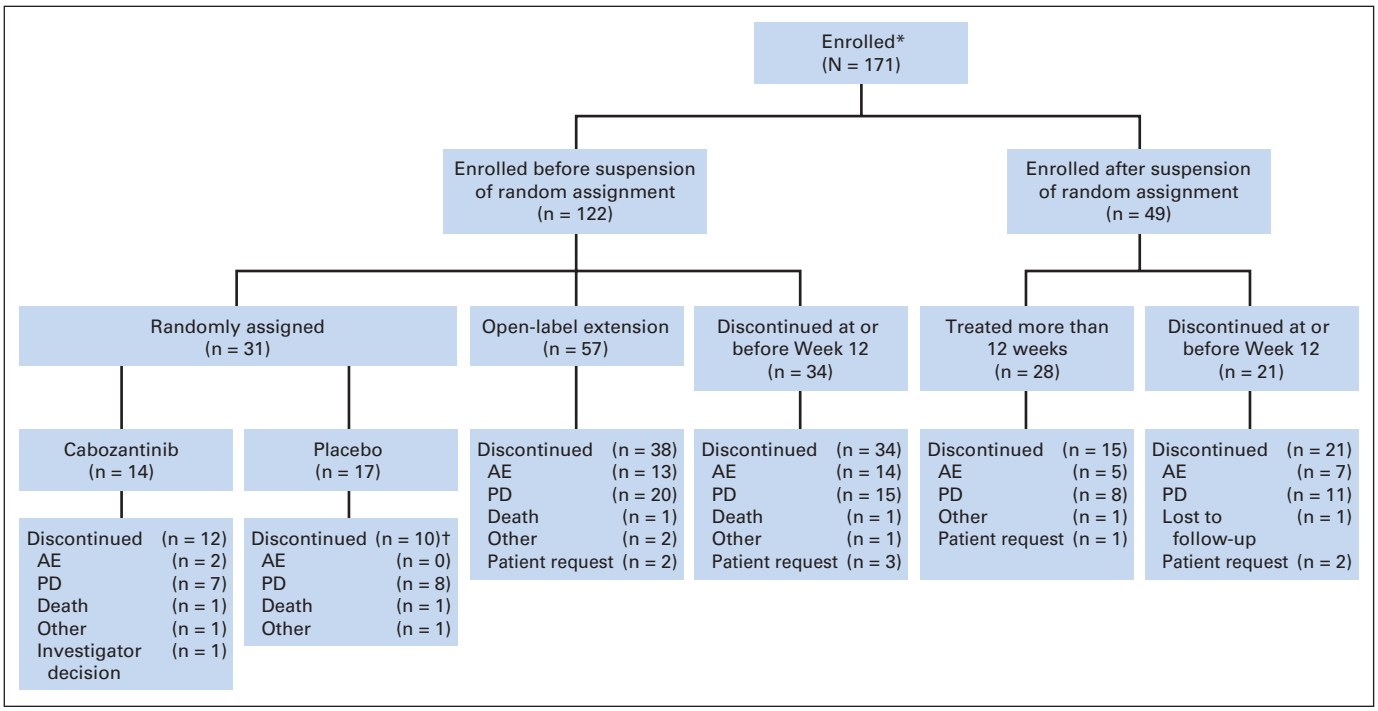

Fig 1. CONSORT diagram, including enrollment, random assignment, and open-label treatment of study patients. (*) Included one patient who did not meet eligibility criteria (no measurable disease). (†) Seven patients who were randomly assigned to placebo and crossed over to open-label cabozantinib treatment after unblinding were still active at the time of data cutoff. AE, adverse event; PD, progressive disease.

Table 2. Response to Treatment

Response	No. of Patients	%
Tumor response*		
No. evaluable	170	
Response		
Confirmed partial response	9	5
Stable disease	127	75
Progressive disease	18	11
Disease control rate at week 12†		66
Bone scan‡		
No. evaluable	116	
Visual read		
Complete resolution		12
Partial resolution		56
Stable disease		28
Progressive disease		3
Pain§		
No. evaluable	83	
Pain improvement at week 6 or week 12		67
Narcotic use‖		
No. evaluable	55	
Decrease or discontinuation		56
Bone turnover markers		
No. evaluable for serum tALP (≥ 2× ULN at baseline)¶	30	
≥ 50% decrease in tALP		57
No. evaluable for plasma CTx#	126	
≥ 50% decrease in CTx		57

NOTE. Percentages may not total 100% because of rounding.
Abbreviations: CTx, cross-linked C-terminal telopeptide of type I collagen; tALP, total alkaline phosphatase; ULN, upper limit of normal.
*Radiographic tumor assessment by investigator using RECIST (version 1.0) during the 12-week lead-in stage. Of 171 enrolled patients, one patient did not have measurable disease at baseline.
†Disease control rate consisting of partial response and stable disease at week 12.
‡Best overall change on bone scan as determined by visual read by an independent radiologist.
§Investigator survey of patients with bone metastases and pain at baseline who had at least one postbaseline assessment.
‖Investigator survey of patients with bone metastases, pain, and narcotic use at baseline who had at least one postbaseline assessment.
¶Patients with bone metastases who had at least reached week 12.
#Patients with bone metastases who had available week 6 and/or week 12 samples analyzed.

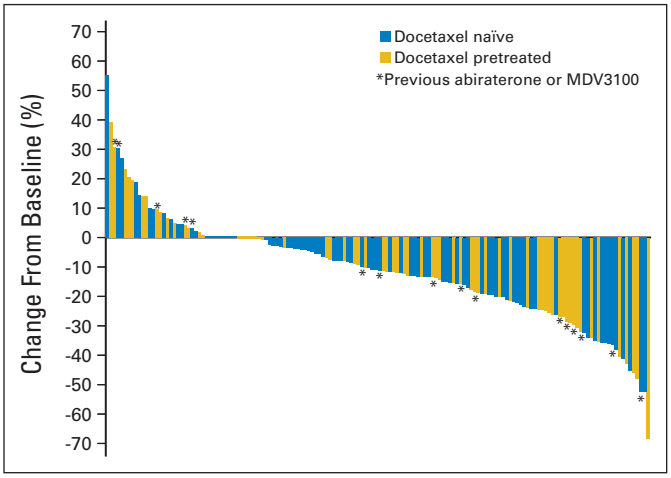

Fig 2. Best changes from baseline in investigator-assessed measurements of tumor lesions in soft tissue using RECIST (version 1.0) in patients with castration-resistant prostate cancer who had measurable disease at baseline and at least one postbaseline radiographic assessment (n = 154). A reduction in the sum of measurable tumor lesions was observed in 72% of patients.

111 (72%) had at least one assessment demonstrating a reduction of soft tissue tumor lesions (Fig 2). Change in measurable disease was independent of prior treatment.

PFS

The primary end point was PFS of patients who had stable disease at week 12 and were randomly assigned to blinded treatment with cabozantinib or placebo. Before suspension of random assignment, 31 patients with CRPC were randomly assigned (14 to cabozantinib and 17 to placebo). A marked increase in PFS (from random assignment) was observed for patients randomly assigned to cabozantinib (median PFS, 23.9 weeks) compared with placebo (median PFS, 5.9 weeks; hazard ratio, 0.12; $P < .001$; Fig 3A).

The median overall PFS for the entire treatment period from the start of the study (week 1, day 1) including all cabozantinib-treated patients (n = 171) was estimated using the piecewise method[22] to be 29.4 weeks. The median PFS was 29.7 weeks for patients who were docetaxel naive (n = 97) and 23.9 weeks for patients who previously received a docetaxel-based therapy (n = 74; Fig 3B).

Exploratory Analyses

Prompted by the observation of bone scan improvement, post hoc analyses of the effects of cabozantinib on bone scan, bone markers, pain and narcotic use, and PSA were performed.

Bone scan. One hundred forty-nine patients had evidence of bone metastases at baseline, and 116 patients (78%) had at least one follow-up bone scan evaluable for response. Bone scans were improved in 79 patients (68%), with complete resolution in 14 patients (12%) and partial resolution in 65 patients (56%); stable disease was observed in 33 patients (28%) and progressive disease in four patients (3%; Table 2). Representative images of patients with bone scan improvement are shown in Figure 4.

Bone markers. Markers of bone formation (serum tALP) and bone resorption (plasma CTx) were analyzed in stored blood specimens from patients with bone metastases. Forty-three patients had baseline levels of tALP at least 2× ULN. Of the 30 patients who reached week 12, 27 had declines in tALP ranging from 9% to 83%, with reductions of 50% or more in 17 (57%) of 30 patients (Table 2; Appendix Fig A2A, online only). Decreases from baseline CTx levels were observed in 108 of 126 patients who had at least one follow-up assessment, with reductions of 50% or more in 72 (57%) of 126 patients (Table 2; Appendix Fig A2B). Changes in both tALP and CTx were independent of prior and/or concurrent bisphosphonate therapy.

Bone pain. Baseline pain was reported by 92 men with bone metastases, with 71 men taking narcotics to control the pain (Table 1). Among patients with at least one available postbaseline assessment of pain or narcotic use, 67% (56 of 83 patients) reported an improvement in pain control with a decrease in or discontinuation of narcotics by 56% (31 of 55 patients; Table 2).

PSA. PSA changes did not correlate with the antitumor effects in bone and soft tissue (Appendix Fig A3, online only), suggesting that

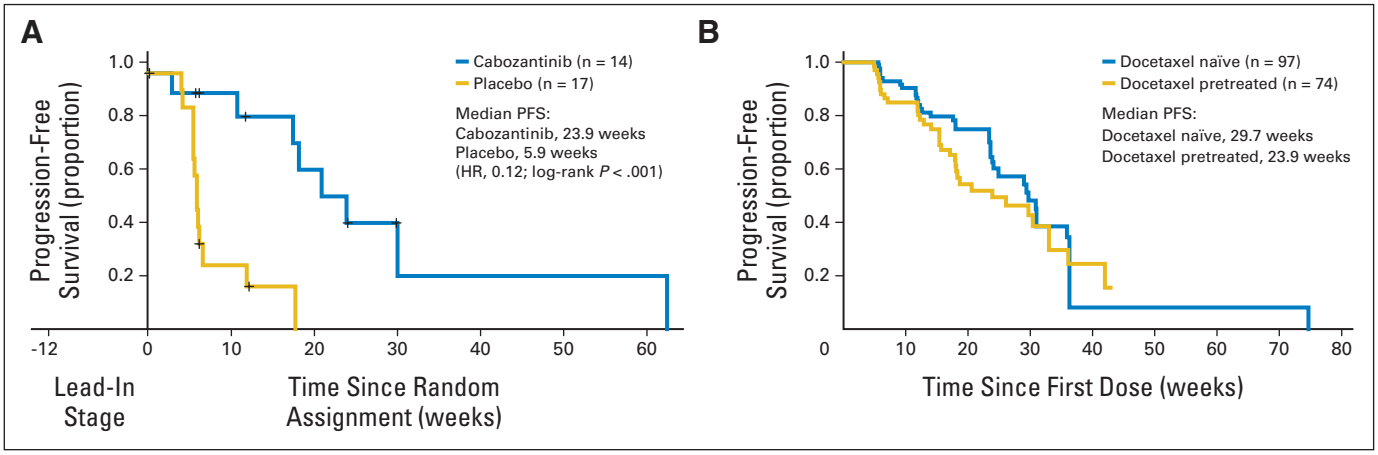

Fig 3. Kaplan-Meier estimates of progression-free survival (PFS) in (A) randomly assigned patients with castration-resistant prostate cancer (CRPC) and (B) patients with CRPC by docetaxel pretreatment status. Panel A shows the probability of PFS from week 12 random assignment for patients with CRPC randomly assigned to continued treatment with cabozantinib (n = 14) or placebo (n = 17). Panel B shows the probability of PFS for all patients with CRPC (n = 171) by docetaxel pretreatment status from first dose of cabozantinib. HR, hazard ratio.

PSA is not a reliable surrogate of clinical outcome in the context of treatment with cabozantinib.

Association of Bone Scan Findings With Other Clinical Parameters

Bone scan improvement was associated with other measures of antitumor effect and clinical benefit (Appendix Fig A4, online only). More patients with complete or partial resolution of bone scans, compared with patients with either stable or progressive bone scans, had regression of measurable soft tissue disease (81% *v* 61%, respectively) and CTx decrease ≥ 50% (62% *v* 48%, respectively); in addition, patients with complete or partial resolution of bone scans demonstrated a higher PFS rate at 6 months (56% *v* 41%, respectively). Moreover, among patients with bone pain and narcotic use at baseline, those with bone scan resolution, compared with those without resolution, were more likely to experience pain relief (93% *v* 35%, respectively) and reduced narcotic use (72% *v* 23%, respectively).

Safety

Adverse events irrespective of causality reported in ≥ 10% of patients during the lead-in stage of the study are listed in Table 3. All patients had at least one adverse event, and the majority of patients experienced more than one. The most common all-grade adverse events were a variable cluster of symptoms consisting of fatigue, decreased appetite, taste alterations, nausea, diarrhea, weight loss, and palmar-plantar erythrodysesthesia (hand-foot syndrome), which resulted in dose reductions in 62% of patients (106 of 171 patients). These events typically responded promptly to drug interruption and dose reduction. The most common grade ≥ 3 adverse events were fatigue (16%), hypertension (12%), palmar-plantar erythrodysesthesia (8%), dehydration (8%), pulmonary embolism (7%), decreased appetite (6%), and nausea (5%). One patient died while on study treatment (unexplained death). The most common serious adverse events were pulmonary embolism (6%) and dehydration and vomiting (each 5%).

DISCUSSION

Bone is the major site of metastatic disease in men with prostate cancer, and bone metastases provide the most significant clinical challenges in the management of patients with CRPC. In this study, cabozantinib demonstrated dramatic and rapid effects on bone scan lesions

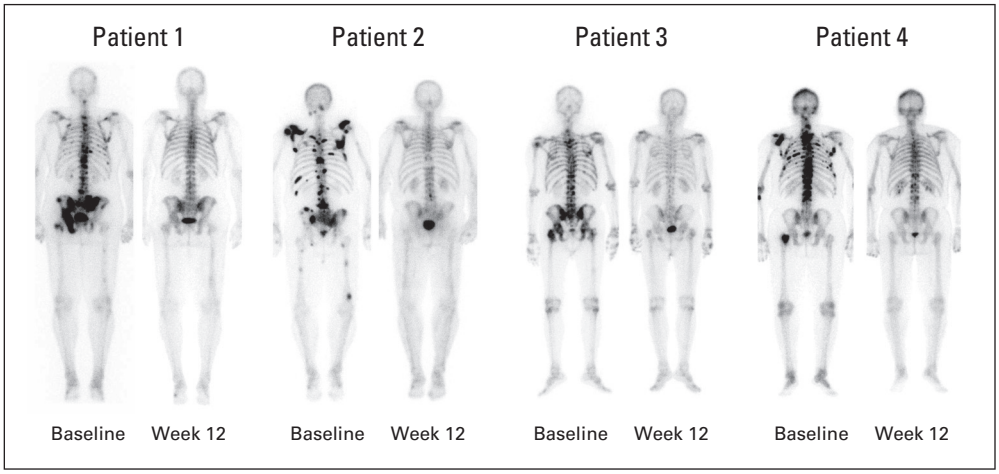

Fig 4. Bone scan effects of cabozantinib treatment on study patients. Sequential whole-body technetium methylene diphosphonate bone scintigraphy is shown of four patients with advanced metastatic prostate cancer. Baseline scans show multiple areas of increased radiotracer uptake indicative of extensive bone metastases. Treatment with cabozantinib resulted in complete or partial resolution of bone scans at week 12. Bone scan resolution correlated with partial response of tumor lesions in soft tissue and pain relief in each patient.

Table 3. Most Frequently Reported Adverse Events During Lead-In Stage Regardless of Causality (N = 171)

Adverse Event	All Grades		Grade ≥3	
	No. of Patients	%	No. of Patients	%
Fatigue	108	63	27	16
Decreased appetite	93	54	10	6
Diarrhea	87	51	5	3
Nausea	83	49	8	5
Weight decreased	58	34		
Constipation	57	33	1	1
PPE syndrome	52	30	13	8
Dysgeusia	50	29		
Dysphonia	50	29		
Vomiting	48	28	6	4
Hypertension	38	22	21	12
Mucosal inflammation	36	21	2	1
Asthenia	34	20	7	4
Dyspnea	28	16	4	2
Hypothyroidism	25	15		
Abdominal pain	24	14	5	3
Rash	23	13	2	1
Cough	22	13	1	1
Dehydration	19	11	13	8
AST increased	19	11	5	3
Dizziness	19	11	1	1
Stomatitis	19	11	1	1
Dyspepsia	18	11	1	1
Dry mouth	18	11		
Oral pain	18	11		
Gastroesophageal reflux disease	17	10		
Insomnia	17	10		

NOTE. For the most frequently reported adverse events (≥ 10%), three grade 4 events were reported (pain, abdominal pain, and AST increased).
Abbreviation: PPE, palmar-plantar erythrodysesthesia.

in a high proportion of patients. The effects seen on bone scan are echoed in other measures of antitumor effect. Although the response rate measured by RECIST is relatively low (5%), four out of five of these men with progressive measurable disease at baseline had at least stable soft tissue disease at the 12-week time point, and more than 70% had a decrease in the measurements of their soft tissue lesions. The objective changes in soft tissue lesions seem to correlate with a decrease in uptake on bone scan in the majority of patients treated, but the effects in bone and soft tissue seem to occur independently of a change in PSA. Cabozantinib-treated patients showed consistent effects on markers of bone formation and resorption, bone pain, and narcotic use, and in the randomly assigned cohort, statistically significant improvement in PFS was seen with cabozantinib compared with the placebo group.

The observed effects on bone scan are unprecedented in the treatment of CRPC. The actual mechanism of the reduction in uptake on bone scan seen in these patients remains unclear. Uptake of radiotracer in bone depends on blood flow and osteoblastic activity, and decreased uptake may be attributable to interruption of blood flow, direct modulation of osteoblastic activity, direct effect on the tumor cells, or a combination of these processes. Only occasional cases of decreased uptake on bone scan in men with CRPC have been reported in clinical trials with other VEGF/VEGFR-targeted therapies, abiraterone, docetaxel, or dasatinib, and no changes in bone lesions were reported in a trial using a selective MET inhibitor.[23-27] These results suggest that selectively targeting VEGFR alone, VEGF alone, MET alone, or the tumor cells and/or osteoclasts individually does not result in the bone scan effects observed in patients with CRPC treated with cabozantinib.[28] The correlations between bone scan and changes in soft tissue, along with the reductions of bone turnover markers and independence of prior bisphosphonate therapy, suggest that cabozantinib has direct effects on tumor cells and the bone microenvironment. Further studies including direct sampling of tissues will be required to define the pathways involved in these effects and to assess the antitumor effects.

The results from this cohort of men with metastatic CRPC raise several additional important questions. On the basis of the unexpected improvement on bone scans coupled with substantial improvements in reported pain and the observation that men randomly assigned to placebo had rapid recurrence of symptoms related to bone disease, the SOC concluded that it was unethical to continue random assignment in this cohort. The result of this decision is a small randomly assigned population. Although the results from the randomized cohorts are suggestive of benefit, PFS is difficult to measure in CRPC, and the impact of therapy on overall survival is unknown. True benefit will only be determined from randomized trials, and phase III studies (Cabozantinib MET Inhibition CRPC Efficacy Trial [COMET] 1 and 2) have been initiated to evaluate the effect of cabozantinib on morbidity and mortality in patients with CRPC with bone metastases. The positive effects on bone and soft tissue lesions were demonstrated in the context of adverse effects, which, while typical of tyrosine kinase inhibitors, resulted in frequent dose reductions. Strategies for the management of these adverse effects and evaluation of alternate dosing regimens will be required. The improvement in bone pain and decrease in narcotic use with cabozantinib treatment were from a retrospective chart review that cannot assess the balance between decreased pain and adverse effects of therapy. The impact of cabozantinib on the quality of life of men with CPRC will require prospective evaluation of patient-reported outcomes using standardized measures.

In conclusion, this study demonstrates that cabozantinib has substantial antitumor activity in patients with advanced CRPC with manageable toxicity consistent with other tyrosine kinase inhibitors targeting multiple pathways. These results indicate a potential cooperative role for c-MET and VEGF signaling in the progression of CRPC and suggest that dual targeting of tumor and microenvironment may lead to an improved outcome for patients with CRPC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Genitourinary Cancer: Prostate

Repurposing Itraconazole as a Treatment for Advanced Prostate Cancer: A Noncomparative Randomized Phase II Trial in Men With Metastatic Castration-Resistant Prostate Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Itraconazole • Prostate cancer • Angiogenesis • Hedgehog pathway

ABSTRACT

Background. The antifungal drug itraconazole inhibits angiogenesis and Hedgehog signaling and delays tumor growth in murine prostate cancer xenograft models. We conducted a noncomparative, randomized, phase II study evaluating the antitumor efficacy of two doses of oral itraconazole in men with metastatic prostate cancer.

Patients and Methods. We randomly assigned 46 men with chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC) to receive low-dose (200 mg/day) or high-dose (600 mg/day) itraconazole until disease progression or unacceptable toxicity. The primary endpoint was the prostate-specific antigen (PSA) progression-free survival (PPFS) rate at 24 weeks; a 45% success rate in either arm was prespecified as constituting clinical significance. Secondary endpoints included the progression-free survival (PFS) rate and PSA response rate (Prostate Cancer Working Group criteria). Exploratory outcomes included circulating tumor cell (CTC) enumeration, serum androgen measurements, as well as pharmacokinetic and pharmacodynamic analyses.

Results. The high-dose arm enrolled to completion ($n = 29$), but the low-dose arm closed early ($n = 17$) because of a prespecified futility rule. The PPFS rates at 24 weeks were 11.8% in the low-dose arm and 48.0% in the high-dose arm. The median PFS times were 11.9 weeks and 35.9 weeks, respectively. PSA response rates were 0% and 14.3%, respectively. In addition, itraconazole had favorable effects on CTC counts, and it suppressed Hedgehog signaling in skin biopsy samples. Itraconazole did not reduce serum testosterone or dehydroepiandrostenedione sulfate levels. Common toxicities included fatigue, nausea, anorexia, rash, and a syndrome of hypokalemia, hypertension, and edema.

Conclusion. High-dose itraconazole (600 mg/day) has modest antitumor activity in men with metastatic CRPC that is not mediated by testosterone suppression. ***The Oncologist*** 2013;18:163–173

Implications for Practice: This study investigated two doses of an oral antifungal drug, itraconazole, to determine whether it has antitumor activity in men with metastatic castration-resistant prostate cancer. The results showed that while low-dose itraconazole (200 mg/day) did not have significant antitumor effects, high-dose itraconazole (600 mg/day) did have some activity in these patients. Moreover, the effects of itraconazole appeared to be associated with inhibition of Hedgehog signaling in skin biopsies, and were not caused by testosterone suppression. Therefore, itraconazole may be a non-hormonal treatment option for patients with castration-resistant prostate cancer who wish to prevent or delay the use of chemotherapy. While itraconazole is not as effective as other novel agents for advanced prostate cancer (*e.g.* abiraterone, enzalutamide), it is a generic drug that may be considered if the cost of these newer agents is prohibitive, or in parts of the world where abiraterone and enzalutamide may not be available.

INTRODUCTION

Although androgen-deprivation therapy is very effective initial therapy for men with advanced prostate cancer, all patients will eventually progress to a state known as castration-resistant prostate cancer (CRPC), which is invariably fatal. Until recently, life-prolonging therapies for patients with metastatic CRPC were limited, consisting only of docetaxel chemotherapy [1]. In the past 2 years, three additional modalities were added to our armamentarium for metastatic CRPC: the autologous immu-

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notherapy product sipuleucel-T [2], the chemotherapy agent cabazitaxel [3], and the novel androgen-biosynthesis inhibitor abiraterone [4]. Moreover, two additional agents (the bone-targeting radiopharmaceutical radium-223 [5] and the androgen-signaling inhibitor enzalutamide [6]) were recently reported to extend survival in these patients. Despite these advances, none of these therapies are curative, and survival times for men with metastatic CRPC remain short (20–24 months) [7]. In this light, novel biological targets continue to be explored [8] in order to expand treatment options for men with CRPC.

Drug development is a lengthy and expensive process, taking, on average, 15 years and US$80 million to bring a single drug to market [9]. To increase the efficiency of this process, a drug library comprising >3,000 existing compounds has been created, enabling in vitro screening of old drugs for novel biological functions [10]. This drug library was recently screened for agents that may inhibit angiogenesis, a potentially important target of prostate cancer therapeutics [11]. An unexpected "hit" from this screen was the antifungal agent itraconazole, which was found to inhibit endothelial cell proliferation in vitro (unlike other azole antifungals) [12] and to impede endothelial cell migration and capillary tube formation [13]. Although its antiangiogenic target is uncertain, one study suggested that itraconazole inhibits mammalian target of rapamycin in endothelial cells by impairing cholesterol trafficking [14]. In vivo, itraconazole was found to inhibit neovascularization in a mouse Matrigel™ (BD Biosciences, San Diego, CA) model, to delay tumor growth in a castration-resistant xenograft mouse model (22Rv1), and to inhibit metastases in the AT6.3 prostate cancer mouse model [12]. Intriguingly, itraconazole was also discovered to potently inhibit Hedgehog (Hh) signaling, a developmental pathway regulating epithelial–mesenchymal interactions, cell survival, and angiogenesis [15]. To this end, in vitro studies showed that itraconazole inhibited proliferation of the Hh reporter cell line Shh-Light2 by antagonizing Smoothened [16]. Additionally, itraconazole induced tumor growth inhibition in a mouse medulloblastoma model (Ptch$^{+/-}$ p53$^{-/-}$) with constitutive overactivation of Hh signaling. In this allograft model, itraconazole downmodulated intratumoral expression of *GLI1*, a Hh target gene [16].

Because itraconazole is already approved by the U.S. Food and Drug Administration (FDA) as an antifungal agent at oral doses in the range of 200–600 mg/day [17], we conducted a phase II study examining the antitumor efficacy of two doses of itraconazole (200 mg/day and 600 mg/day) in men with metastatic CRPC. This study was prompted by the encouraging clinical activity of other antiangiogenic agents in CRPC patients [18] and by other data suggesting that upregulation of Hh pathway components may drive CRPC [19]. In addition, the cost of generic itraconazole is only a fraction of that of other novel therapies for CRPC, such as abiraterone and enzalutamide.

Patients and Methods

Patients

Our target population was men with metastatic CRPC who had not received cytotoxic chemotherapy. Patients were required to have histologically confirmed prostate adenocarcinoma, progressive disease despite "castration levels" of serum testosterone (<50 ng/dL), and radiographically visible distant metastases on computed tomography (CT) or technetium-99 bone scans. Patients had to have three or more rising serum prostate-specific antigen (PSA) values taken 4 weeks apart with the last value being ≥2.0 ng/mL, in accordance with Prostate Cancer Working Group (PCWG) guidelines [20]. Other eligibility criteria included age >18 years, an Eastern Cooperative Oncology Group (ECOG) performance status score ≤2, a life expectancy >6 months, and adequate kidney, liver, and bone marrow function.

Patients were excluded if they had received an oral antiandrogen within 6 weeks, had ever received chemotherapy for metastatic CRPC, took systemic corticosteroids, had a malabsorption syndrome, took drugs metabolized by cytochrome P450 (CYP)3A4, had a prior malignancy within 3 years, had major infectious, pulmonary, or cardiac illnesses, had symptomatic congestive heart failure, or had a corrected QT interval >450 msec on electrocardiography. Prior ketoconazole treatment was permitted.

The review boards at all institutions approved the study, which was conducted according to good clinical practice guidelines. All patients provided written informed-consent.

Study Design

This was a noncomparative, open-label, randomized, phase II study conducted at four institutions of the Prostate Cancer Clinical Trials Consortium [21]. Patients were randomized (1:1) to receive low-dose (200 mg/day) or high-dose (600 mg/day) itraconazole. These doses were chosen because itraconazole is already FDA approved as an antifungal agent at doses in the range of 200–600 mg/day and because data from animal models suggested that, although 200 mg might be sufficient to inhibit angiogenesis, doses ≥600 mg might be required to suppress Hh signaling.

Itraconazole was supplied as generic 100-mg capsules (Sandoz, Princeton, NJ). Patients assigned to the low-dose arm received two 100-mg capsules once daily; patients in the high-dose arm received three 100-mg capsules twice daily. Because itraconazole absorption depends on gastric acidity, patients were instructed to take itraconazole capsules with a carbonated beverage and together with food or within 30 minutes after a meal. Patients were not permitted to take concurrent antacids, histamine blockers, or proton pump inhibitors. Treatment continued either until unmanageable drug-related toxicity or until clinical or radiographic progression. Importantly, treatment was not discontinued for PSA elevations [20].

Assessments

Clinical evaluations included a physical examination, vital sign measurements, assessment of ECOG score, review of concomitant medications, laboratory evaluations (chemical and hematologic studies), and review of adverse events and were performed every 4 weeks. Efficacy assessments included serum PSA measurement every 4 weeks and CT (chest, abdomen, and pelvis) and whole-body technetium-99 bone scan evaluations every 12 weeks.

Outcome Measures

The primary endpoint was freedom from PSA progression (the PSA progression-free survival [PPFS] rate) at 24 weeks after randomization. PSA progression was defined as a ≥25% increase in PSA from nadir (and by ≥2 ng/mL), requiring confirmation ≥4 weeks later (PCWG criteria) [20]. Although the PPFS rate is not a validated surrogate of clinical benefit, this endpoint was chosen in order to screen for preliminary evidence of clinical activity in the setting of a small phase II trial. A key secondary endpoint,

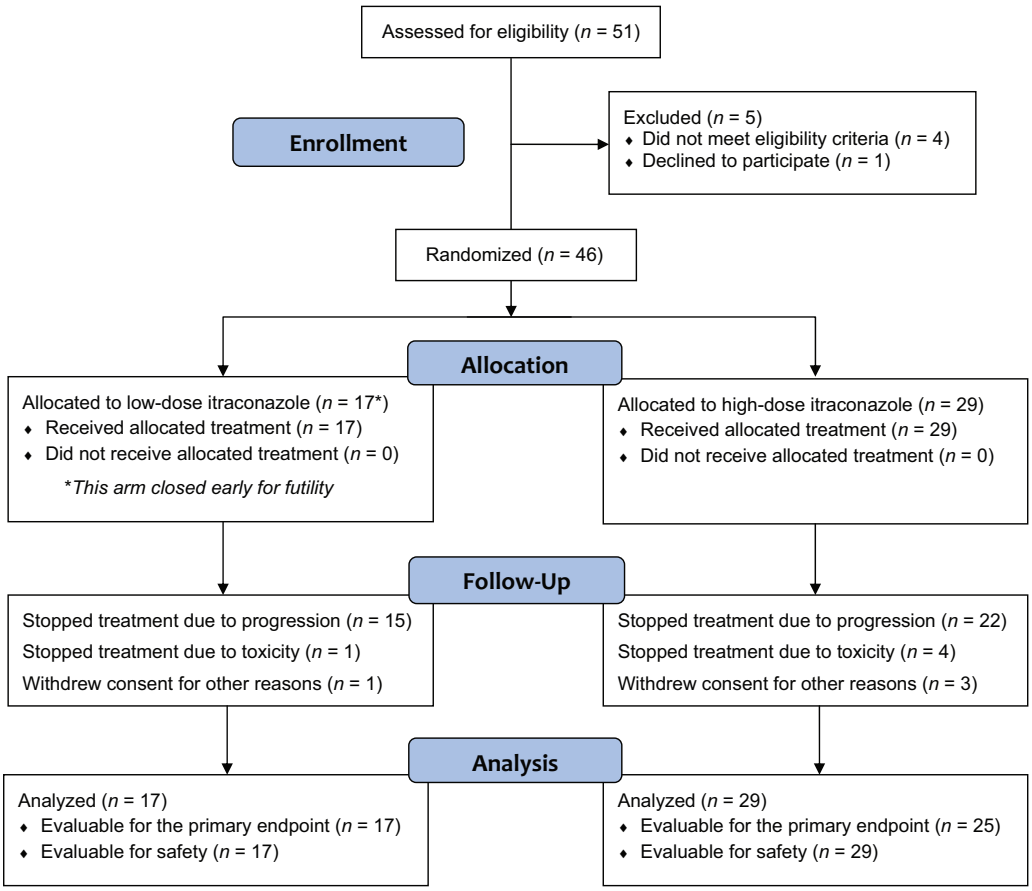

Figure 1. Consort diagram.

which might be considered more clinically meaningful, was freedom from progression (the progression-free survival [PFS] rate) at 24 weeks. Progression was defined [20] as clinical progression (worsening disease-related symptoms or new cancer-related complications), radiographic progression (on CT scan, ≥20% enlargement in the sum diameter of soft-tissue target lesions according to the Response Evaluation in Solid Tumors [RECIST], version 1.0 [22]; on bone scan, two or more new confirmed bone lesions), or death, whichever occurred first.

Secondary endpoints included the median PPFS duration, PSA response rate (≥50% PSA decline from baseline, maintained for ≥4 weeks), best PSA response (maximal percentage PSA decrease from baseline), median PFS time, and objective response rate in measurable soft-tissue lesions (partial response, ≥30% decrease in the sum diameter of target lesions; progressive disease, ≥20% increase in the sum diameter of target lesions or one or more new lesion; stable disease, change in the sum diameter of target lesions that do not meet the above parameters; RECIST, version 1.0 [22]). A final secondary endpoint was safety; adverse events were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Circulating Tumor Cell Analysis

Blood samples (7.5 mL) for circulating tumor cell (CTC) enumeration were collected at baseline and after 4 weeks and 12 weeks on study and were analyzed using the CellSearch® system (Veridex, Raritan, NJ), as previously described [23]. Results were expressed as numbers of CTCs per 7.5 mL blood.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

Plasma samples were collected at baseline and prior to itraconazole administration (minimum concentration [C_{min}]) and at 4 weeks and 12 weeks on study. Itraconazole and 4-hydroxyitraconazole concentrations were assessed using a validated liquid chromatography–mass spectrometry assay, over the range of 2–2,000 ng/mL.

Analysis of Adrenal Axis

To examine whether or not itraconazole suppressed adrenal cortical function, several adrenal-axis hormones were evaluated at baseline and after 4 weeks and 12 weeks on study: testosterone, dehydroepiandrostenedione sulfate (DHEA-S), cortisol, aldosterone, and adrenocorticotropic hormone (ACTH). Serum testosterone and serum aldosterone were measured using a liquid chromatography–mass spectrometry assay. Using this method, the lower limit of detection of testosterone is 1 ng/dL. Serum DHEA-S and plasma ACTH levels were measured using a chemiluminescence immunoassay. Serum cortisol was measured using an enzyme immunoassay.

Vascular Endothelial Growth Factor Levels

To evaluate antiangiogenic effects in an exploratory analysis, plasma was collected for vascular endothelial growth factor (VEGF) measurement at baseline and after 4 weeks and 12 weeks on study. Total VEGF concentrations were measured using the Quantikine® enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).

Table 1. Baseline demographic and clinical characteristics

	Low-dose: 200 mg/day ($n = 17$)		High-dose: 600 mg/day ($n = 29$)		
Baseline characteristic	***n***	**%**	***n***	**%**	***p*-value**
Median (range) age, yrs	73 (60–81)		71 (52–89)		.30
Race					
White	10/17	58.8	21/29	72.4	.52
Nonwhite	7/17	41.2	8/29	27.6	
Mean (range) Gleason score	7.4 (5–9)		7.6 (5–10)		.51
Median (range) baseline PSA, ng/mL	29.2 (7.0–1,989.5)		43.5 (2.6–234.5)		.18
Median (range) baseline PSA doubling time, mos	2.7 (1.4–6.8)		2.4 (0.9–10.7)		.75
ECOG performance status score					
0	11/17	64.7	18/29	62.1	.99
1 or 2	6/17	35.3	11/29	37.9	
Metastatic sites					
Bone only	3/17	17.7	12/29	41.4	.37
Visceral/soft tissue only	5/17	29.4	6/29	20.7	
Bone and visceral/soft tissue	9/17	52.9	11/29	37.9	
Mean (range) number of metastases	6.5 (1–27)		5.5 (1–14)		.51
Mean (range) number prior hormonal therapies	2.6 (1–5)		2.5 (1–5)		.85
Prior ketoconazole					
Yes	5/17	29.4	9/29	31.0	.99
No	12/17	70.6	20/29	69.0	
Median (range) baseline testosterone, ng/dL	5 (1–20)		6 (1–26)		.41
Median (range) baseline hemoglobin, g/dL	12.5 (9.0–14.7)		13.0 (9.9–15.0)		.29
Median (range) baseline albumin, g/dL	4.0 (3.5–5.0)		4.1 (3.4–4.7)		.83
Median (range) baseline alkaline phosphatase, U/L	99 (55–454)		89 (47–733)		.64

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen.

Hh Pathway Analysis

Because Hh signaling is present in skin and hair follicles, we examined GLI1 mRNA expression (a marker of Hh pathway activation) using 3-mm skin punch biopsies from hair-containing skin obtained at baseline and after 4 weeks and 12 weeks on study. RNA was extracted from skin biopsy specimens, and *GLI1* expression levels were assessed by real-time reverse-transcription polymerase chain reaction (SABiosciences-Qiagen, Frederick, MD), as previously described [24].

Statistical Analysis

Based on prior studies [25], we estimated that up to 20% of patients with metastatic CRPC who had not received prior chemotherapy would be free from PSA progression (as defined above) after 24 weeks on study. We hypothesized that itraconazole (at either dose level) would prevent PSA progression at 24 weeks in ~45% of men (i.e., we considered a 25% absolute improvement >20% to be clinically meaningful). Twenty-nine patients per arm would grant 83% power to detect an improvement in the 24-week PPFS rate (the primary endpoint) from 20% (historical controls) to 45% using a two-sided α of 0.05. A 45% 24-week PPFS rate in each arm was predefined to constitute a success (indicating worthiness for further study). To monitor for treatment futility, both arms had prespecified early-stopping rules that were applied after nine (one third of the total) and 15 (one half of the total) patients were evaluable for the primary endpoint. In each arm, if there were fewer than two of nine men who achieved the primary endpoint or if there were fewer than four of 15 men who achieved the primary endpoint, then that arm would close for futility. These stopping rules were consistent with observing an upper bound of a one-sided exact 90% confidence interval (CI) that excluded our hypothesized success rate of 45%.

The study was not powered to allow inferential statistics comparing treatment arms. Kaplan–Meier analysis was used to estimate time-to-event endpoints and 95% CIs. Patient baseline characteristics were compared between arms using Fisher's exact test, Student's *t*-test, or the Wilcoxon rank-sum test (*p*-values are merely descriptive because all differences are a result of chance variation induced by randomization). Pharmacodynamic and pharmacokinetic endpoints were reported as trends over time using descriptive statistics; associations between these exploratory measures and clinical outcomes were sought using Pearson's correlation coefficient (*r*).

Results

Patients

The high-dose arm was enrolled to completion (29 patients) whereas the low-dose arm closed early because of futility after 17 men were enrolled (in this arm, there were two successes in the first nine patients and enrollment continued until 15 were evaluable for the primary endpoint; at that time, two additional patients were enrolled but no more achieved the

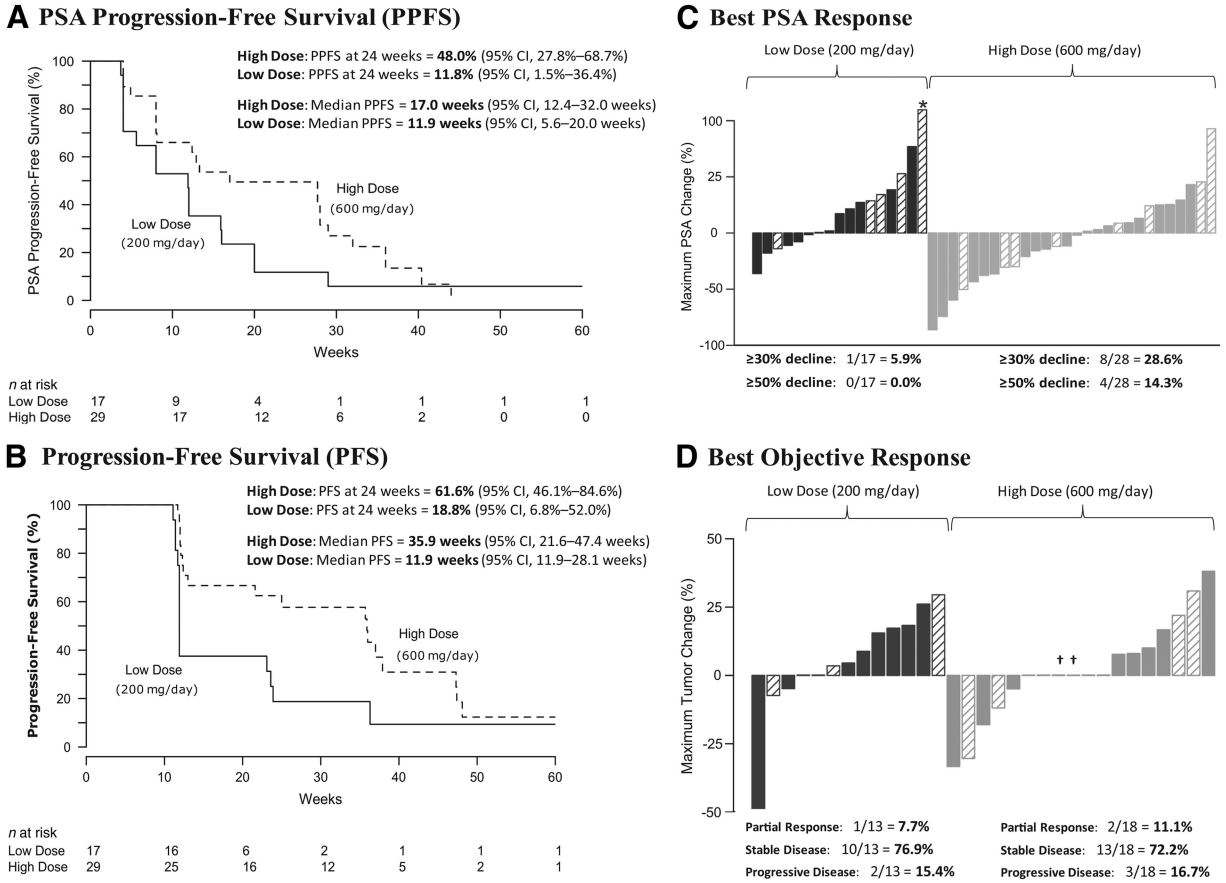

Figure 2. Clinical effects of itraconazole. **(A):** Kaplan–Meier curves of PPFS in men receiving low-dose and high-dose itraconazole. **(B):** Kaplan–Meier curves of PFS in each treatment arm. **(C):** Waterfall plots showing best PSA responses among men receiving low-dose and high-dose itraconazole. The asterisk denotes a clipped PSA value. Prior treatment with ketoconazole is indicated by the hashed bars. **(D):** Waterfall plots showing best objective responses in measurable lesions according to Response Evaluation Criteria in Solid Tumors, version 1.0. Prior treatment with ketoconazole is indicated by the hashed bars (and daggers).

Abbreviations: CI, confidence interval; PFS, progression-free survival; PPFS, PSA progression-free survival; PSA, prostate-specific antigen.

primary endpoint) (Fig. 1). Baseline patient characteristics appeared generally balanced (Table 1); there was a trend toward lower baseline PSA levels in the low-dose arm and a trend toward more bone-only metastases in the high-dose arm. One third of patients in both arms had received prior ketoconazole. The median treatment durations were 11.9 weeks in the low-dose arm and 23.6 weeks in the high-dose arm.

Primary Endpoint

All 17 patients in the low-dose arm and 25 of 29 patients in the high-dose arm (four men came off study before 24 weeks because of toxicity) were evaluable for the primary endpoint. In the low-dose arm, the 24-week PPFS rate estimate was 11.8% (two of 17 men; 95% CI, 1.5%–36.4%), failing to achieve the primary endpoint. Conversely, the high-dose arm met the primary endpoint, demonstrating a 24-week PPFS rate estimate of 48.0% (12 of 25 men; 95% CI, 27.8%–68.7%).

Secondary Endpoints

The median PPFS times were 11.9 weeks (95% CI, 5.6–20.0 weeks) and 17.0 weeks (95% CI, 12.4–32.0 weeks) in the low-dose and high-dose arms, respectively (Fig. 2A). The 24-week PFS rate estimates were 18.8% (95% CI, 6.8%–52.0%) and 61.6% (95% CI, 46.1%–84.6%) in the two arms, respectively. The median PFS times were 11.9 weeks (95% CI, 11.9–28.1 weeks) and 35.9 weeks (95% CI, 21.6–47.4 weeks) (Fig. 2B). PSA response rates (≥50% PSA decline) were 0% (95% CI, 0%–19.5%) and 14.3% (95% CI, 4.0%–32.7%) (Fig. 2C), respectively. Among those with measurable disease at baseline, 7.7% (95% CI, 1.8%–33.9%) and 11.1% (95% CI, 3.4%–33.1%) of patients in the two arms achieved a partial objective response, respectively (Fig. 2D). Finally, the median PSA doubling time (PSADT) estimates were longer in both study arms after treatment initiation, although this change was only statistically significant in the high-dose arm (baseline median PSADT, 2.4 months; on-study median PSADT, 7.7 months; difference, +5.3 months; $p < .01$) and not in the low-dose arm (baseline median PSADT, 2.7 months; on-study median PSADT, 5.8 months; difference, +3.1 months; $p = .07$).

Safety

Adverse events were generally more frequent in the high-dose than in the low-dose arm (Table 2). Common toxicities in both arms included fatigue, pain, nausea and constipation. Also, a constellation of adverse events comprising hypertension, hypokalemia, and edema was of special interest, suggesting a syndrome of secondary mineralocorticoid excess (see adrenal-axis evaluations below). Manifestations of this syndrome were more frequent in the high-dose arm.

Grade 3 adverse events in the low-dose arm included fatigue (5.9%), anorexia (5.9%), and rash (5.9%). Grade 3 toxici-

Table 2. Adverse events

	Low-dose: 200 mg/day ($n = 17$)				High-dose: 600 mg/day ($n = 29$)			
Adverse event	**All grades**	**%**	**Grade 3**	**%**	**All grades**	**%**	**Grade 3**	**%**
Fatigue	9	52.9	1	5.9	15	51.7		
Pain	7	41.2			13	44.8		
Nausea	4	23.5			11	37.9		
Constipation	2	11.8			10	34.5		
Edema (peripheral)	4	23.5			10	34.5		
Hypertension	0	0.0			9	31.0	2	6.9
Diarrhea	1	5.9			8	27.6		
Anorexia	2	11.8	1	5.9	7	24.1		
Headache	2	11.8			6	20.7		
Rash	3	17.6	1	5.9	5	17.2	1	3.4
Vomiting	2	11.8			5	17.2		
Dyspnea	1	5.9			5	17.2		
Hypokalemia	0	0.0			5	17.2	3	10.3
Urinary frequency	4	23.5			4	13.8		
Hot flashes	3	17.6			4	13.8		
Cough	3	17.6			3	10.3		
Peripheral neuropathy	3	17.6			3	10.3		
Dizziness	0	0.0			3	10.3		
Dry mouth	0	0.0			3	10.3		
Infection (respiratory)	0	0.0			3	10.3		
Taste alteration	0	0.0			3	10.3		

ties in the high-dose arm included hypokalemia (10.3%), hypertension (6.9%), and rash (3.4%). There were no grade 4 toxicities. The percentages of patients who came off study as a result of toxicities were 5.9% in the low-dose arm (one patient developed a rash) and 13.8% in the high-dose arm (one patient developed fatigue, one patient developed anorexia, one patient developed a rash, and one patient developed temporal arteritis [not drug related]).

CTC Enumeration

Fifteen patients in the low-dose arm (88.2%) and 25 patients in the high-dose arm (86.2%) had paired baseline and post-treatment blood samples collected for CTC enumeration. Thirty-two men had favorable baseline CTC counts (<5 CTCs per 7.5 mL blood); 96.9% of them retained favorable CTC counts for 12 weeks. Eight men had unfavorable baseline CTC counts (≥ 5 CTCs per 7.5 mL blood); five (62.5%) of them converted to favorable CTC counts post-treatment. Data from those patients converting from unfavorable to favorable CTC counts are shown here: 28→3, 15→1, 7→0, 6→0, and 6→0 CTCs per 7.5 mL blood.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

Sixteen patients in the low-dose arm (94.1%) and 26 patients in the high-dose arm (89.7%) had paired baseline and post-treatment plasma samples for pharmacokinetic analyses. The mean plasma itraconazole trough concentration (C_{min}) values were 370.0 ng/mL (range, 86.9–653.1 ng/mL) and 1,517.0 ng/mL (range, 673.8–2,360.2 ng/mL) in low- and high-dose arms, respectively. The mean plasma 4-hydroxyitraconazole C_{min} values were 723.5 ng/mL (range, 289.2–1,157.8 ng/mL) and 2,630.8 ng/mL (range, 1,036.0–4,225.6 ng/mL), respectively. There were significant correlations between a higher itraconazole C_{min} level and both a longer PPFS duration ($r = 0.56$; $p = .003$) and a greater PSA decline ($r = 0.39$; $p = .03$) (supplemental online Fig. 1). Similar statistically significant correlations were observed with 4-hydroxyitraconazole (data not shown).

Adrenal Axis Analysis

Neither low-dose nor high-dose itraconazole caused suppression of serum testosterone or DHEA-S levels. Unexpectedly, low-dose and high-dose itraconazole appeared to slightly increase serum testosterone (Fig. 3A) and DHEA-S (Fig. 3B) levels, respectively. Additionally, high-dose (but not low-dose) itraconazole potently suppressed serum aldosterone (Fig. 3C) while raising plasma ACTH (Fig. 3D). There were no effects with either itraconazole dose on serum cortisol at 4 weeks or 12 weeks (data not shown).

VEGF Analysis

Low-dose itraconazole was not associated with a change in plasma VEGF level at either 4 weeks ($p = .59$) or 12 weeks ($p = .11$). Likewise, high-dose itraconazole was not associated with a VEGF level change at either 4 weeks ($p = .72$) or 12 weeks ($p = .76$).

Hh pathway analysis

Fifteen patients in the low-dose arm (88.2%) and 25 patients in the high-dose arm (86.2%) had paired baseline and post-treatment skin punch biopsy samples collected for *GLI1* expression analysis. *GLI1* was downmodulated in 33% and 68% of patients in the low- and high-dose arms, respectively (Fig. 4A). The per-

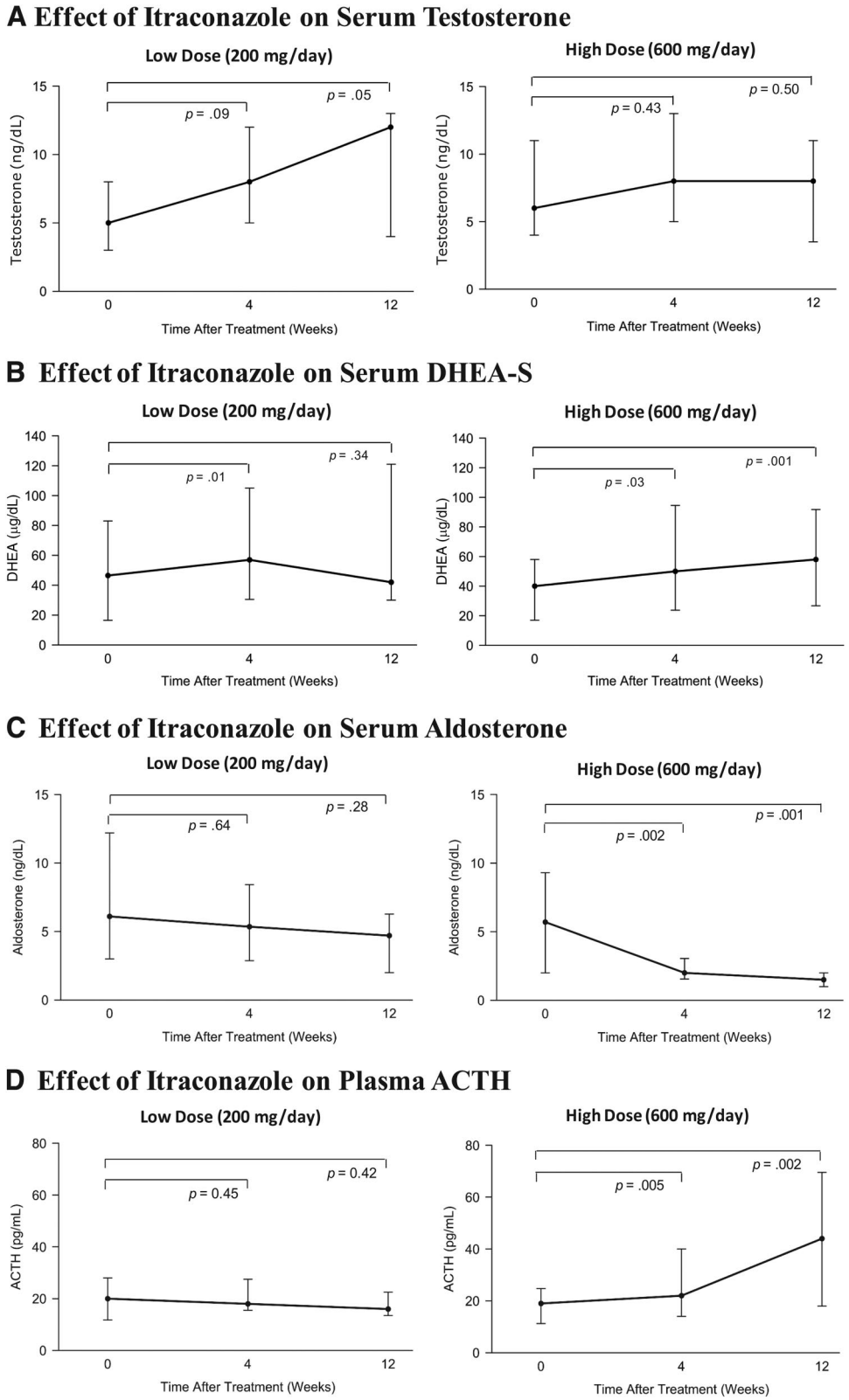

Figure 3. Endocrine effects of itraconazole. **(A):** Effect of low- and high-dose itraconazole on serum testosterone concentrations (data are shown as medians and interquartile ranges). **(B):** Effect of low- and high-dose itraconazole on serum DHEA-S concentrations. **(C):** Effect of low- and high-dose itraconazole on serum aldosterone concentrations. **(D):** Effect of low- and high-dose itraconazole on plasma ACTH concentrations.

Abbreviations: ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrostenedione-sulfate.

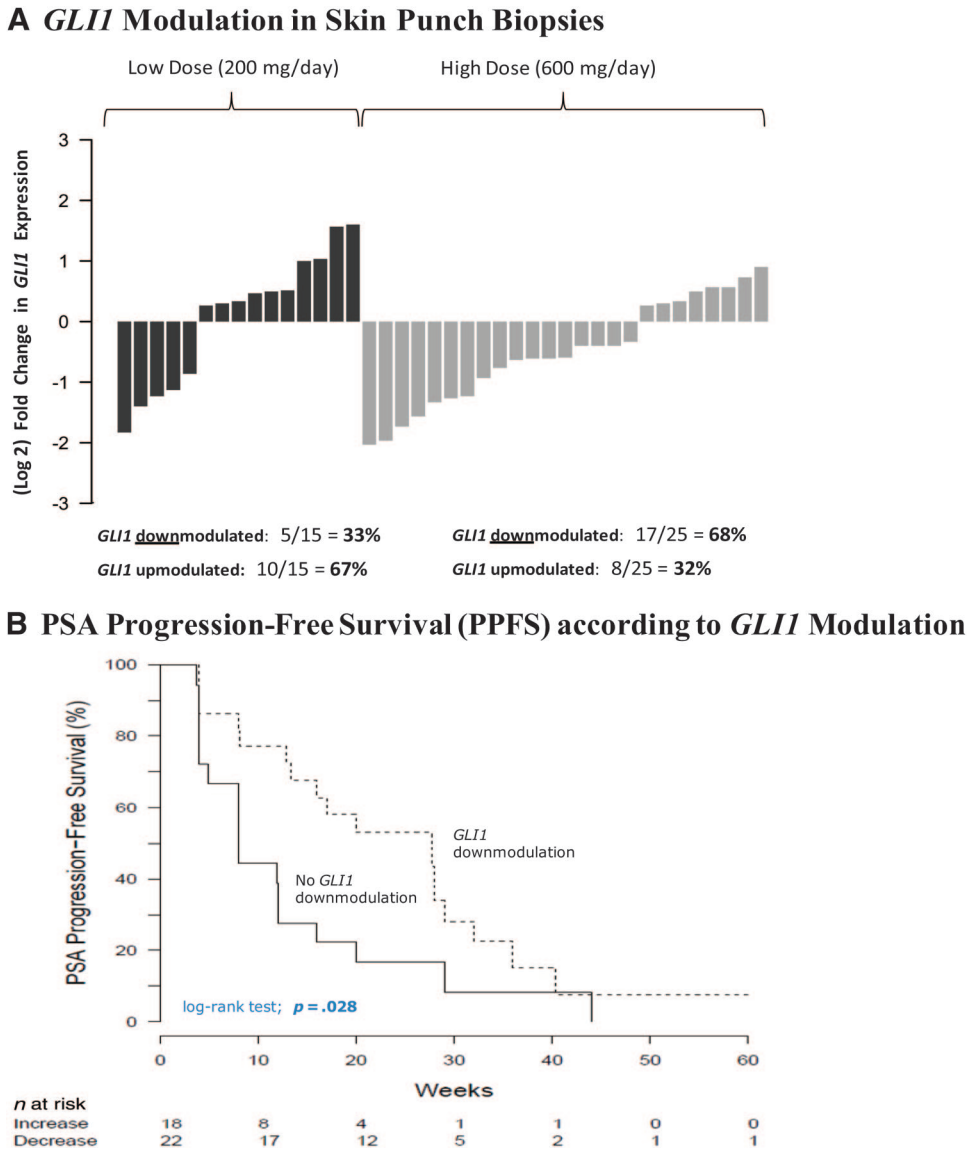

Figure 4. *GLI1* modulation by itraconazole. **(A):** Waterfall plots showing *GLI1* modulation in skin punch biopsies, depicted as fold change in *GLI* expression post-treatment compared with baseline values. **(B):** Kaplan–Meier curves depicting PPFS according to *GLI1* modulation status. **(C):** Kaplan–Meier curves depicting PFS according to *GLI1* modulation status. **(D):** Scatterplot showing the association between *GLI1* modulation and PSA change.

Abbreviations: PFS, progression-free survival; PPFS, PSA progression-free survival; PSA, prostate-specific antigen.

centage of patients who achieved a twofold or greater downmodulation in *GLI1* with itraconazole was 28% (11 of 40), compared with 68% of patients receiving vismodegib (a potent Hh pathway antagonist) in prior studies [26]. The median PPFS time was longer in men who achieved *GLI1* downmodulation ($p = .028$) (Fig. 4B) and there was also a trend toward a longer PFS interval in men with *GLI1* downmodulation ($p = .128$) (Fig. 4C). Finally, there was a significant correlation between a stronger *GLI1* downmodulation and a greater PSA decline ($r = 0.38$; $p = .01$) (Fig. 4D). Interestingly, all five patients who achieved favorable CTC conversions also had downmodulation of *GLI1*.

Discussion

This phase II study is the first to examine itraconazole as an antineoplastic agent in human cancer. We demonstrate that, in men with metastatic chemotherapy-untreated CRPC, low-dose itraconazole (200 mg/day) lacks significant antitumor efficacy, whereas high-dose itraconazole (600 mg/day) may have modest clinical activity, as suggested by longer PPFS and PFS times than in historical data [25]. Importantly, the PFS duration observed here (35.9 weeks) is comparable with PFS time estimates (range, 30–40 weeks) of other FDA-approved and experimental agents in this patient population (mitoxantrone, docetaxel, tasquinimod, and cabozantinib) [1, 18, 27], although the PFS time is not a surrogate of clinical benefit. Notably, itraconazole's activity does not appear to be mediated by testosterone suppression (although a comprehensive analysis of the androgen axis was not conducted), and it may possibly be associated with downmodulation of Hh signaling. Alternatively, itraconazole may have beneficial off-target effects on other unknown targets.

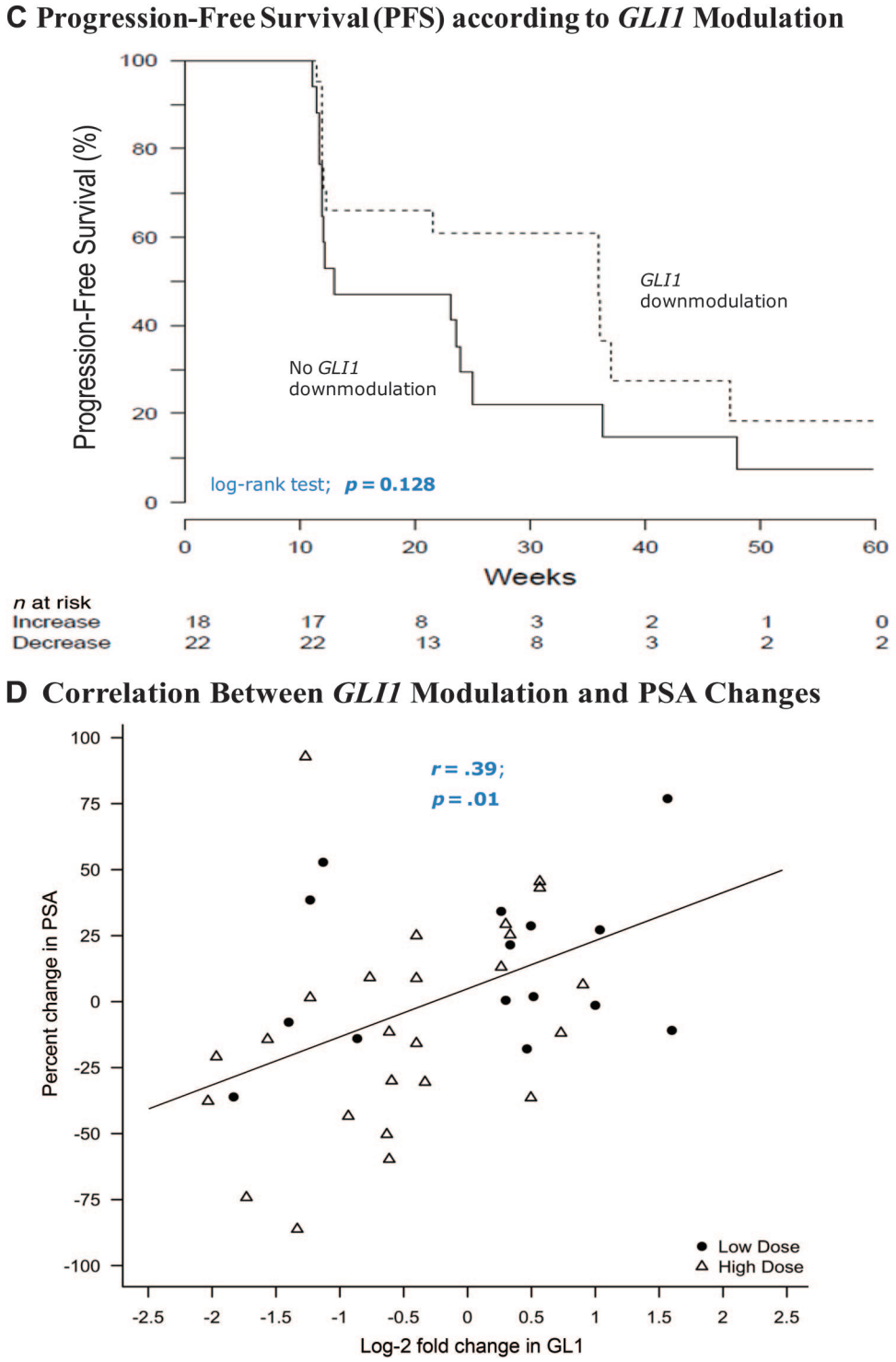

Figure 4. Continued.

Another azole antifungal, ketoconazole, has been used off label for many years as a therapy for CRPC. Ketoconazole functions by suppressing extragonadal androgen synthesis [28] (nonselectively inhibiting multiple CYP enzymes), but carries significant toxicity without evidence that it extends the survival duration [29]. However, the selective CYP17 inhibitor abiraterone was shown to improve survival outcomes in men with docetaxel-pretreated metastatic CRPC, [4], resulting in its FDA approval. Here, we demonstrate that itraconazole does not suppress circulating testosterone or DHEA-S levels (although androstenedione and dihydrotestosterone levels were not measured), suggesting an alternative or additional antitumor mechanism. Moreover, itraconazole appeared to have activity in both ketoconazole-pretreated and ketoconazole-naïve patients.

Tumor angiogenesis and Hh signaling are both involved in prostate cancer growth, progression, and metastasis [15, 30]. Although blocking each pathway separately has failed to yield

new prostate cancer therapeutics [26, 31], inhibition of both pathways simultaneously with itraconazole represents a rational approach. In this study, we did not observe modulation of circulating VEGF levels, but that does not necessarily mean that itraconazole lacks antiangiogenic effects in man. Our ability to interrogate angiogenesis was limited by the lack of tumor biopsy samples and because we evaluated only one of many circulating angiogenic factors (although none have consistently been associated with clinical benefit from antiangiogenic therapies). Additionally, although we observed *GLI1* downmodulation in skin biopsy samples, we did not interrogate Hh signaling in tumors themselves; therefore, we provide only indirect evidence that Hh pathway suppression is a potential mechanism of action of itraconazole. Finally, the association between *GLI1* downmodulation and itraconazole's clinical activity may not be causal, and it may simply reflect a pharmacodynamic effect that is not linked to drug efficacy. Nevertheless, the results of this study provide the impetus to examine other more potent Hh pathway inhibitors (e.g., vismodegib, LDE225) in men with CRPC.

Of particular interest was the occurrence of a syndrome of hypokalemia, hypertension, and edema in a dose-dependent manner. Although these manifestations are usually related to hyperaldosteronism [32], aldosterone levels were potently suppressed in our patients. This raises the possibility of a syndrome of secondary mineralocorticoid excess (with elevated aldosterone precursors), as has been reported in abiraterone-treated patients [4, 33]. To this end, we discovered raised levels of corticosterone and deoxycorticosterone in a patient who developed all three features of this syndrome. However, unlike abiraterone (and ketoconazole), itraconazole did not suppress cortisol production and does not require glucocorticoid supplementation. Indeed, the combination of itraconazole and corticosteroids is contraindicated and can induce Cushing's syndrome by impairing corticosteroid metabolism by CYP3A4 [34]. Finally, the slight rises observed in serum testosterone and DHEA-S levels may have resulted from elevation of upstream ACTH, although these increases in androgen levels were modest.

In conclusion, this study suggests that high-dose itraconazole (600 mg/day) may have modest antitumor activity in men with metastatic CRPC that could potentially be associated with Hh pathway suppression, although an androgen-mediated effect cannot be excluded. Ongoing trials are now assessing the impact of itraconazole as an antineoplastic agent in patients with lung cancer, breast cancer, and basal cell carcinoma. Future studies in prostate cancer patients will compare itraconazole with placebo in men with nonmetastatic CRPC, aiming to extend the metastasis-free survival duration in this population. In addition, clinical trials using more potent Hh antagonists (e.g., vismodegib, LDE225) in men with CRPC are also being planned.

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PHASE I STUDIES

Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer

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Summary Androgen receptor-mediated transcription is directly coupled with the induction of DNA damage, and castration-resistant tumor cells exhibit increased activity of poly (ADP-ribose) polymerase (PARP)-1, a DNA repair enzyme. This study assessed the efficacy and safety of low dose oral PARP inhibitor veliparib (ABT-888) and temozolomide (TMZ) in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer (mCRPC) in a single-arm, open-label, pilot study. Patients with mCRPC progressing on at least one docetaxel-based therapy and prostate specific antigen (PSA) ≥2 ng/mL were treated with veliparib 40 mg twice daily on days 1–7 and TMZ once daily (150 mg/m^2/day cycle 1; if well tolerated then 200 mg/m^2/day cycle 2 onwards) on days 1–5 q28 days. Patients received 2 (median) treatment cycles (range, 1–9). The primary endpoint was confirmed PSA response rate (decline≥30 %). Twenty-six eligible patients were enrolled, 25 evaluable for PSA response. Median baseline PSA was 170 ng/mL. Two patients had a confirmed PSA response (8.0 %; 95 % CI: 1.0–26.0), 13 stable PSA, and 10 PSA progression. The median progression-free survival was 9 weeks (95 % CI: 7.9–17) and median overall survival 39.6 weeks (95 % CI: 26.6–not estimable). The most frequent treatment-emergent adverse events (AEs) were thrombocytopenia (77 %), anemia (69 %), fatigue (50 %), neutropenia (42 %), nausea (38 %), and constipation (23 %). Grade 3/4 AEs occurring in >10 % of patients were thrombocytopenia (23 %) and anemia (15 %). Veliparib and TMZ combination was well tolerated but with modest activity. Biomarker analysis supported the proof of concept that this combination has some antitumor activity in mCRPC.

Keywords Pilot study · Metastatic castration-resistant prostate cancer · Veliparib · Temozolomide · Combination therapy

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Introduction

The anticancer effect of many cancer therapeutics is mediated through DNA damage, leading to cell cycle arrest and apoptosis. Agents that inhibit DNA repair proteins are of

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significant clinical interest, primarily to potentiate the effects of cytotoxic therapies and other DNA damaging agents as well as monotherapy in tumors with defects in DNA repair. Of the poly (ADP-ribose) polymerase (PARP) family of proteins, PARP-1 and -2 play a role in DNA repair of single-strand DNA breaks via the base-excision repair mechanism [1–3]. PARP activity appears to be increased in some tumors [4, 5] and therefore represent a potential therapeutic target. Continuous inhibition of PARP-1 results in conversion of single-strand to double-strand breaks during DNA replication, thus stalling the process of replication [3]. PARP knockout mice are hypersensitive to alkylating agents and ionizing radiation [6–8]. Furthermore, clinical evidence indicates that PARP inhibitors have antitumor activity as monotherapy in DNA repair-deficient tumors due to mutations in *BRCA1* and *BRCA2* [9–12], and there is evidence of increased antitumor effect when added to cytotoxic chemotherapy [13, 14]. PARP-1 has been implicated at the chromatin level in androgen receptor-mediated cell proliferation in early- and late-stage prostate cancer models [15], with suppression of PARP-1 resulting in reduced cell proliferation.

Veliparib (ABT-888) is an orally bioavailable, well-tolerated, potent PARP inhibitor with a favorable pharmacokinetic profile [14, 16–18]. In *in vitro* and *in vivo* models, veliparib increased the sensitivity of prostate cancer cells to radiation therapy and chemotherapy, including the oral alkylating agent, temozolomide (TMZ) [19–23]. Veliparib also reversed resistance to TMZ in a mouse model of prostate cancer and resulted in improved survival [21]. The maximum tolerated oral dose of veliparib and TMZ 150–200 mg/m^2/day in a phase 1 dose-escalation study in patients with solid tumors (NCT00526617) was 40 mg BID. Human pharmacokinetics indicated that an oral dose of 40 mg BID would achieve exposures consistent with the preclinically maximally efficacious dose [24]. Based on these data, it was hypothesized that combination veliparib and TMZ will have antitumor activity in patients with metastatic castration-resistant prostate cancer (mCRPC).

Patients and methods

Study design

This multicenter, open-label, single-arm, pilot study was carried out between April 21, 2010 and July 6, 2011 at 5 sites in the US according to the regulations and guidelines of the International Conference on Harmonization for Good Clinical Practice and the US Food and Drug Administration, the ethical principles of the Declaration of Helsinki, and all applicable local regulations (ClinicalTrials.gov trial registration ID: NCT01085422). The protocol and all study-related information for participants were reviewed by an independent ethics committee or review board at each site.

Patient eligibility

Eligible patients had mCRPC with measurable and/or bony disease that had progressed despite androgen deprivation therapy and at least 1, but no more than 2, prior systemic non-hormonal therapies (at least 1 including docetaxel). Additional inclusion criteria were prostate specific antigen (PSA) progression (defined as a rising trend in PSA that was confirmed by another assessment at a minimum interval of 1 week), a minimum PSA of 2 ng/mL, and testosterone <50 ng/dL. Patients were required to continue androgen deprivation therapy with a luteinizing hormone-releasing hormone analog if they had not undergone orchiectomy. Subjects were also required to have adequate bone marrow, renal and hepatic function, evaluated within 2 weeks prior to treatment initiation: absolute neutrophil count (ANC) ≥1,500/μL, platelets ≥ 100,000/μL, hemoglobin ≥9.0 g/dL; serum creatinine ≤1.5× upper limit of normal (ULN) or creatinine clearance ≥50 mL/min/1.73 m^2; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN. For subjects with liver metastases, the required values were AST and ALT <5×ULN and bilirubin ≤1.5×ULN. All patients underwent baseline disease evaluation with a chest X-ray or chest computed tomography (CT), a CT scan of the abdomen and pelvis, and a bone scan.

Exclusion criteria included: cord compression or a history of uncontrolled central nervous system metastases or leptomeningeal disease; prior therapy with dacarbazine, or TMZ, or a PARP inhibitor; prior therapy with an investigational agent or any anticancer therapy within 28 days prior to study drug administration (subjects receiving bisphosphonate therapy were eligible); another active malignancy within the past year with the exception of definitely treated carcinomas *in situ*, superficial bladder cancer, and non-melanoma carcinoma of the skin; clinically significant and uncontrolled major medical condition(s) or any medical condition that in the opinion of the investigator placed the subject at an unacceptably high risk for toxicity.

All participants provided institutional review board-approved written informed consent prior to initiation of any study-related procedures.

Treatment

Patients were treated with oral veliparib 40 mg twice daily (BID) on days 1 through 7 (all cycles) and oral TMZ once daily (QD) on days 1 through 5 in 28-day cycles. TMZ was given at a dose of 150 mg/m^2/day in cycle 1. If this dose was well tolerated (platelets ≥100,000/μL; ANC ≥1,500/μL; no grade 3/4 non-hematological toxicities per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.0), the dose could be escalated to 200 mg/m^2/day in cycle 2 onward. If the TMZ dose was not

escalated in cycle 2, then the dose was not escalated in later cycles. Treatment could be taken for up to 24 cycles and was continued per protocol until disease progression (based on radiographic assessment and Response Evaluation Criteria in Solid Tumors [RECIST Version 1.0], clinical assessment, or pain), unacceptable toxicity, or subject/physician decision.

Dose reductions

Dose reductions or delays were permitted if required. If grade 3/4 toxicity was experienced that was not attributable to TMZ or the underlying disease, treatment was held until resolution to grade ≤1. For grade 3/4 toxicities attributed to veliparib, veliparib was reduced to 20 mg BID then 10 mg BID. If toxicity persisted at 10 mg BID, treatment was discontinued. If grade 3/4 toxicities attributable to TMZ were experienced, treatment was held until resolution, and the dose was reduced by 50 mg/m^2/day in the next cycle. Treatment was discontinued if this dose reduction was not sufficient. The next cycle was not started until the ANC was ≥1,500/μL and the platelet count was ≥100,000/μL. Discontinuation of TMZ or veliparib automatically resulted in discontinuation of the other study drug.

Efficacy assessments

The primary endpoint was confirmed PSA response rate (proportion of patients with a complete or partial PSA response). A complete response was defined as undetectable PSA (≤ 0.2 ng/mL) that was confirmed at least 4 weeks later and a partial response as a PSA decline of ≥30 % that was confirmed at least 4 weeks later. The choice for this endpoint was based on data indicating a 3-month PSA decline of at least 30 % was a surrogate for survival [25].

PSA was assessed at baseline, day 1 of each cycle, final visit, and the 30-day follow-up visit. Stable PSA was defined as PSA not meeting complete or partial response criteria but with no progression. PSA progression was defined as an increase in PSA of ≥25 % from baseline or nadir and an absolute increase of ≥2 ng/mL that was confirmed at least 4 weeks later.

Secondary endpoints included safety and tolerability of veliparib in combination with TMZ, ORR, PSA response rate at 12 weeks following first dose of study drug, TTP, PFS, and OS.

Tumor assessment was performed at baseline, every 8 weeks, and final visit (unless performed within 4 weeks of the final visit), and comprised a diagnostic chest X-ray or chest CT scan, CT scans of the abdomen and pelvis, and bone scans in subjects with known bone metastasis. Radiographic response was assessed according to RECIST [26]. The objective response rate was defined as the proportion of subjects with measurable disease with a complete or partial objective response according to RECIST.

Time to progression (TTP) was defined as the time from first dose to the earliest date of disease progression, regardless of whether this occurred during treatment or following discontinuation. If a subject did not experience disease progression, data were censored at the date of last assessment. Disease progression was based on pain, radiographic, or clinical assessment but not PSA elevation alone without radiographic or clinical evidence.

Survival information was collected approximately every 3 months after the final visit for a period of up to 18 months. Progression-free survival (PFS) was defined as the time from first dose to the earliest date of disease progression, or death within 56 days of last disease progression assessment if progression did not occur. If there was no progression or death within 56 days of last assessment, the data were censored at the date of last assessment. Overall survival (OS) was defined as time from first dose to death (all causes). For surviving subjects, data were censored at the last known alive date.

Safety assessments

Complete history and physical examination was carried out on days 1 and 15 of cycles 1 and 2, then on day 1 of subsequent cycles. Clinical laboratory tests (chemistry and hematology) were carried out at screening, days 1, 15, and 22 during cycles 1 and 2, then day 1 of subsequent cycles.

Adverse events (AEs) were monitored throughout the study and summarized using the Medical Dictionary for Regulatory Activities Version 14.0. Severity was rated according to the NCI-CTCAE Version 4.0. The relationship of AEs to study drug was also assessed by the investigator as 'probably related', 'possibly related', 'probably not related', or 'not related'.

Pharmacodynamic correlates

Several exploratory biomarker analyses were performed to assess treatment effect and identify tumor-specific alterations in cellular proteins and/or circulating tumor cells. Blood samples for the exploratory assessment of biomarkers were collected prior to dosing on days 1 and 15 of cycle 1, on day 1 of every other cycle, and at final visit. Plasma samples were stored at −70 °C or lower until analysis for quantitative assessment of tumor markers.

Detection of the most common ETS transcription factor genomic rearrangement in prostate cancer, the ETS-related oncogenic transcription factor ERG and the androgen-regulated gene TMPRSS2 gene fusion (ERG: TMPRSS2), was assessed. Analysis was carried out by fluorescence *in-situ* hybridization (FISH), performed using a breakaway probe on circulating tumor cells (CTCs) using the CymoGen Dx

ERG/TMPRSS2 translocation probe set (CymoGen Dx, LLC, Irvine, CA), as previously described [27].

CTCs were measured at baseline and on therapy to provide further information on response to treatment. CTC detection was performed as previously described using the CellSearch® system (Veridex LLC, Raritan, NJ) [28–30].

Levels of the glycoprotein tumor marker, carcinoembryonic antigen (CEA), were measured using automated ARCHITECT enzyme-linked immunosorbent assays (ELISAs; Abbott Diagnostics, Abbott Park, IL).

The relationship between specific changes in these biomarkers and PFS was also assessed. For CTCs, the comparison was decrease versus increase/no change in CTC concentration. For CEA, the comparison was low (<5 ng/mL) vs. high (≥5 ng/mL) concentration at baseline, based on the diagnostic threshold for colorectal cancer. The presence or absence of the common ERG: TMPRSS2 translocations was examined for a correlation with response to combination of TMZ and PARP-1 inhibition by veliparib.

Statistical analysis

The primary objective of this study was PSA response rate in patients with mCRPC treated with veliparib and TMZ. Secondary objectives included assessment of safety and tolerability, tumor response rates, survival data, and exploratory analysis of biomarkers, including CTCs.

Based on the assumption that a PSA response rate of 20 % would be of clinical interest and a PSA response rate of 5 % indicates no benefit, a sample size of 25 subjects would provide 76 % power, with a one-sided type I error rate of 0.1.

All efficacy and safety analyses included all patients who received at least one dose of veliparib.

For overall and 12 week PSA response rate, and objective response rate, the proportion of subjects meeting the prespecified criteria was estimated, and the 95 % confidence interval (CI) calculated based on exact binomial distribution. TTP, PFS and OS were estimated by the Kaplan-Meier method; median times and corresponding 95 % CI are presented.

For the exploratory biomarker analysis, survival curves based on subgroups of circulating tumor cells and CEA were compared using the log-rank test at a significance level of $P \leq 0.05$.

Results

A total of 26 patients were enrolled between April 21, 2010 and July 6, 2011. Baseline demographics are summarized in Table 1. Of the 25 subjects evaluable for response, 23 had received prior therapy with docetaxel, with 18 considered refractory to docetaxel (docetaxel discontinued due to progression). One of these subjects had also received prior therapy with abiraterone, and one had received therapy with enzalutamide. The non-evaluable subject was also considered refractory to docetaxel.

Table 1 Baseline demographics

	N=26
Age in years, median (range)	67.0 (55–81)
Race, *n* (%)	
White	21 (80.8)
Black	5 (19.2)
PSA at study entry in ng/mL, median (range)	170.2 (6.9−4,584.4)
Prior chemotherapy, *n* (%)	
1	19 (73.1)
2	7 (26.9)
Gleason score[a], *n* (%)	
0	1 (4.0)
6−7	9 (36.0)
8−10	15 (60.0)
ECOG PS, *n* (%)	
0	5 (19.2)
1	15 (57.7)
2	6 (23.1)
Measurable disease, *n* (%)	20 (76.9)
Bone disease, *n* (%)	22 (84.6)

[a] *n*=25; data missing for 1 subject

Treatment summary

The median number of cycles was 2 (range, 1–9). Six subjects took less than 80 % of the assigned dose of veliparib during 1 cycle of treatment. Exposure to treatment is detailed in Table 2. The reasons for treatment discontinuation were: AE related to PSA, clinical or radiographic disease progression (*n*=27); AE not related to disease progression (*n*=4); withdrew consent (*n*=1); and other reason (*n*=2). Many subjects had >1 reason for discontinuation.

Dose reductions were required in 5 patients: reduction of both agents due to platelet count decrease (*n*=1); reduction of TMZ due to thrombocytopenia/platelet count decrease (*n*=3) or neutropenia (*n*=1).

Efficacy

The PSA response rate was 8.0 % (95 % CI: 1.0–26.0), based on 2 of 25 patients achieving a confirmed PSA decline of ≥ 30 %. In the remaining 23 patients, 13 patients had stable PSA, and 10 had PSA progression. The best percentage PSA reduction from baseline for each patient is shown in Fig. 1. Overall, 3 of 25 patients achieved a maximum PSA decline of ≥30 % at any time during the first 12 weeks of treatment.

Table 2 Treatment exposure

	N=26
Overall number of cycles, median (min/max)	2 (1/9)
Number of cycles received, *n* (%)	
1	3 (11.5)
2	12 (46.2)
3	3 (11.5)
4	5 (19.2)
5	0
6	1 (3.8)
7	1 (3.8)
8	0
9	1 (3.8)

None of the 16 patients with measurable disease for whom data were available achieved an objective response according to RECIST. The median TTP and the median PFS were both 9 weeks (95 % CI: 8–17) (Fig. 2a). The median OS was 39.6 weeks (95 % CI: 27–could not be estimated) (Fig. 2b); 15 deaths were reported in 26 patients (57.7 %). Mean changes from baseline in ECOG performance status scores were minimal.

Safety

Overall, 25 of 26 patients reported at least 1 treatment-emergent AE. The most common are summarized in Table 3. The majority of AEs were NCI-CTCAE grade 1/2. Grade 3/4 AEs occurring in more than 1 patient were: colitis (7.7 %), fatigue (7.7 %), neutropenia (7.7 %), anemia (15.4 %), and thrombocytopenia (23.1 %). The most common AEs (≥20 % of subjects) that were considered by the investigator at least 'possibly related' to treatment were: nausea (veliparib 34.6 % and TMZ 38.5 %), fatigue (34.6 % and 34.6 %, respectively), and thrombocytopenia (23.1 % and 34.6 %, respectively). Treatment-emergent serious AEs were reported for 7 subjects (26.9 %): colitis (*n*=2), hepatorenal syndrome, hyperglycemia, bone pain, mental status change, hematuria, urinary tract obstruction, epistaxis, and deep vein thrombosis (all *n*=1). Discontinuation due to treatment-emergent AEs occurred in 3 of 26 subjects (11.5 %). One patient had fatal hepatorenal syndrome due to disease progression starting 29 days after the last dose (considered 'probably not related' to study drug).

Exploratory biomarkers

Several exploratory correlative biomarkers were included in this study, including both CTC enumeration and plasma protein markers potentially associated with mCRPC .

At baseline, 15 samples were evaluable for CTC and 14 of 15 patients assessed had detectable CTCs (range: 0–592 CTC/7.5 mL blood). A CTC value of ≥5 CTC has been shown to be a poor prognostic indicator in mCRPC [31]. In this study 13/15 patients had CTC values >5. However, for patients who provided samples both at baseline and cycle 2 day 1, there was a negative correlation between change from baseline in CTCs and PFS. Patients with a decrease in CTCs (from 86.9 to 9.6 CTC/7.5 mL blood) had a PFS of 116 vs. 51.5 days in those with no change/increase (from 238.0 to 372.7 CTC/7.5 mL blood) (P=0.0266) (Fig. 3a).

We also examined a set of tumor markers to determine if the baseline levels for any of these markers correlated with patient response. Of interest was the marker CEA which is commonly used to monitor colorectal cancer. Baseline values of CEA≥5 ng/mL (considererd elevated in colorectal cancer) [32] were correlated with a shorter PFS of 51 vs. 116 days in patients with low baseline CEA concentrations (P<0.0001) (Fig. 3b). Notable, CEA levels did not correlate with the absolute number of CTCs detected at baseline, but 8 of the 16 patients with low baseline CEA also demonstrated a reduction in CTC levels after 1 cycle of therapy.

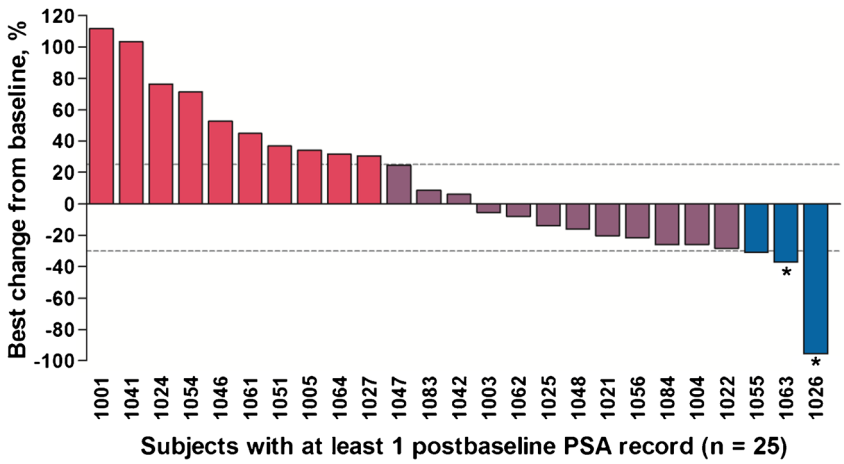

Fig. 1 Best percentage reduction in PSA from baseline at 12 weeks (maximum reduction or minimum increase for subjects with no reduction). One patient was not included due to missing post-baseline assessment. *upper horizontal line*=25 % increase in PSA (disease progression). *lower horizontal line*=30 % decline in PSA (partial response)
*Confirmed partial response

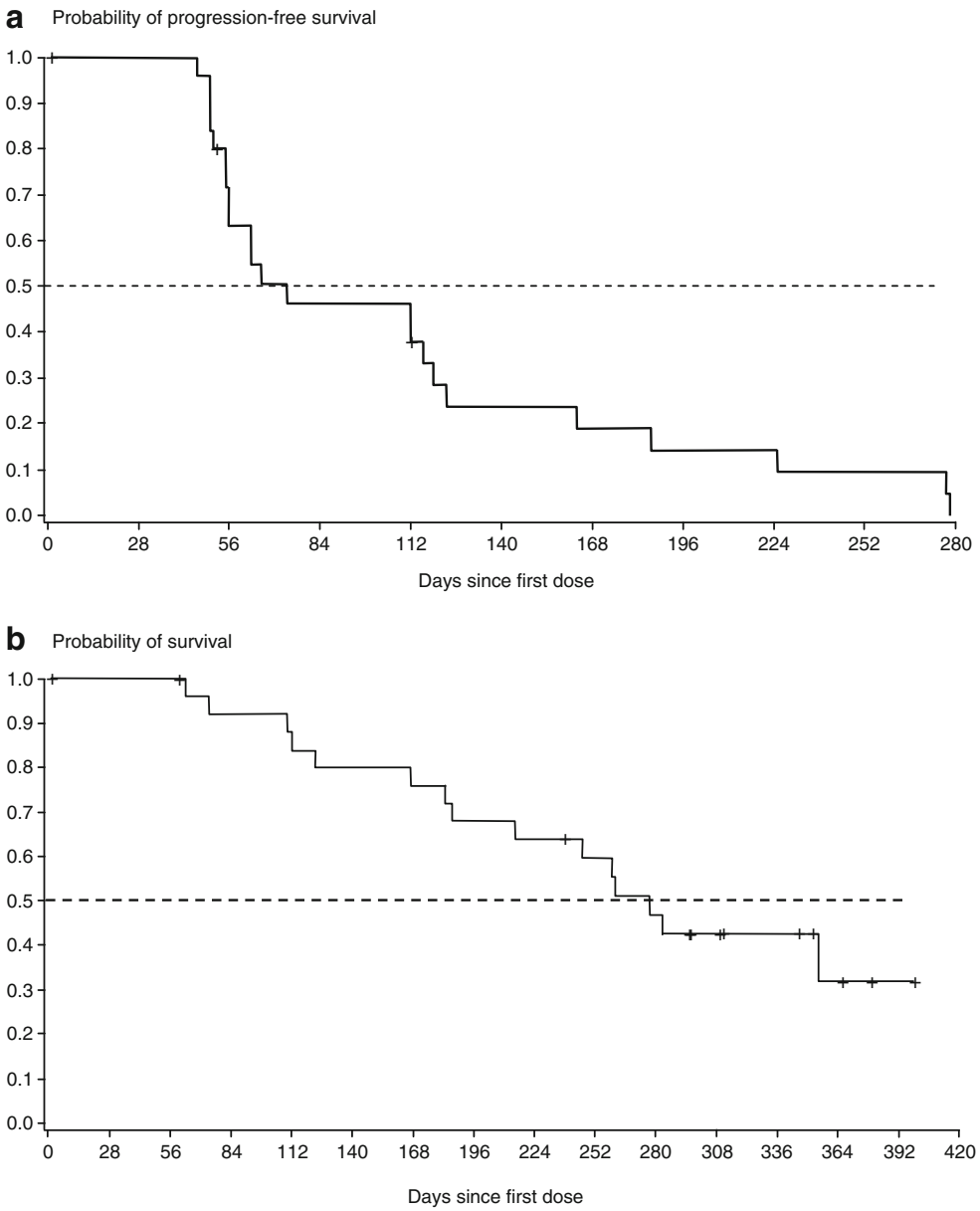

Fig. 2 Kaplan-Meier plots. **a** progression-free survival (radiographic progression and all deaths). **b** overall survival (all deaths)

Approximately 50 % of prostate cancer tissue samples harbor the ERG:TMPRSS2 gene fusion [33, 34], and there is evidence for DNA-independent interaction between ERG: TMPRSS2, PARP-1, and DNA protein kinase [35] Consequently, FISH analysis of CTCs for the ERG:TMPRSS2 gene fusion was performed and was successful in 8 baseline samples; only 1 patient demonstrated clear translocations and 2 patients had no translocation but had large amplifications of the entire region in some CTCs but not in nearby peripheral blood mononuclear cells. The remaining 5 evaluable patients had no translocations or noted amplifications. As only 1 patient tested had the gene fusion, no meaningful correlation with response to treatment could be made; however, this patient achieved stable disease, with a PFS of 70 days and an OS of 277 days.

Discussion

The rationale for combining veliparib and TMZ for the treatment of mCRPC was based on several lines of evidence. First, PARP-1 has been implicated in androgen receptor-dependent cell proliferation in models of both early- and late-stage prostate cancer, with suppression of PARP-1 shown to reduce cell proliferation in these models [15], suggesting that PARP inhibition has the potential to be an effective therapeutic strategy in prostate cancer. Second, veliparib was shown to enhance the activity of chemotherapy in preclinical models of breast cancer and melanoma [16, 22, 23] and to significantly increase the sensitivity of prostate cancer cells to TMZ in an animal model [21], including reversing resistance to TMZ in this

Table 3 Treatment-emergent adverse events occurring in ≥10 % of subjects

		N=26	
		Grade 1/2	Grade 3/4
General	Fatigue	11 (42.3)	2 (7.7)
Gastrointestinal	Nausea	10 (38.5)	0
	Constipation	6 (23.1)	0
	Dysphagia	3 (11.5)	0
	Vomiting	3 (11.5)	0
Hematologic	Thrombocytopenia[a]	14 (53.8)	6 (23.1)
	Anemia[a]	14 (53.8)	4 (15.4)
	Neutropenia[a]	9 (34.6)	2 (7.7)
Musculoskeletal and connective tissue	Pain in extremity	4 (15.4)	0
	Arthralgia	3 (11.5)	0
	Back pain	3 (11.5)	0
	Muscular weakness	3 (11.5)	0
Other	Hypoasthesia	3 (11.5)	0
	Weight decreased	5 (19.2)	0
	Decreased appetite	4 (15.4)	0
	Upper respiratory tract infection	4 (15.4)	0

[a] Includes related blood chemistry and laboratory adverse events

animal model, which translated to improved survival [21]. Third, approximately 50 % of prostate cancer samples harbor the ERG:TMPRSS2 gene fusion [33, 34], and there is evidence for DNA-independent interaction between ERG:TMPRSS2, PARP-1, and DNA protein kinase [35]. PARP-1 blockade has been shown to inhibit the growth of ERG:TMPRSS2-positive prostate cancer xenografts in mice [35], and in another study, inhibition of PARP-1 reduced the number of prostate cancer cells in culture harboring the ERG:TMPRSS2 gene fusion [36].

This study tested the combination of veliparib and TMZ in chemotherapy-pretreated mCRPC patients. This combination was feasible, well tolerated, and the observed AEs were similar to those expected with TMZ monotherapy. Although there was evidence of some antitumor activity, this effect was modest, with 12 % of patients achieving a PSA decline of ≥ 30 % within 3 months, with a median PFS of 9 weeks and median OS of 39.6 weeks.

The overall limited clinical efficacy observed in this study is likely the result of several factors including the chosen relatively lower dose of veliparib maybe a limiting factor; a higher dose might be required for maximum efficacy in this patient population. The veliparib dose used in this trial (40 mg BID) was based on a phase I study of veliparib and TMZ. At this dose, veliparib had no dose-limiting toxicities and achieved a steady-state exposure (area under the plasma concentration-time curve [AUC]) that was effective in murine efficacy models, with no indication of a pharmacokinetic interaction between veliparib and TMZ.

There are other potential reasons for the limited efficacy in this study. If DNA damage is insufficient either due to moderate chemosensitivity of the underlying tumor and/or low DNA damage potential of the chemotherapy, the addition of veliparib may not lead to clinically significant efficacy. Similarly, despite the theoretical rationale and observed preclinical data, the lack of clinical efficacy of single-agent TMZ in patients with mCRPC [37] has likely played a significant role in the observed modest antitumor effect of the combination.

Limitations of the study include the small sample size, and the small number of subjects for whom biomarkers are available, all inherent limitations to a pilot study. The limitations of sample size may have been even more pronounced in the specific sub-populations whom data suggest are uniquely sensitive to PARP-inhibitor therapy, such as BRCA-mutated tumors or tumors with ETS gene fusion.

Current evidence supports a negative association between an on-therapy reduction in CTC levels and progression/survival in prostate cancer [38, 39]. In the present study, the majority of assessable patients had a decrease in CTCs with treatment, which was associated with longer PFS compared with no change or an increase in CTCs. Elevated CEA has been linked with castration resistant prostate cancer and with soft tissue metastatic lesions [40]. Here, longer PFS was observed in patients with low baseline CEA concentrations versus those with high baseline CEA. This is in contrast to a previous study, which found no association between CEA and survival in this disease setting [40]. As only 1 of 8 patients tested had the ERG:TMPRSS2 gene fusion, the hypothesis of

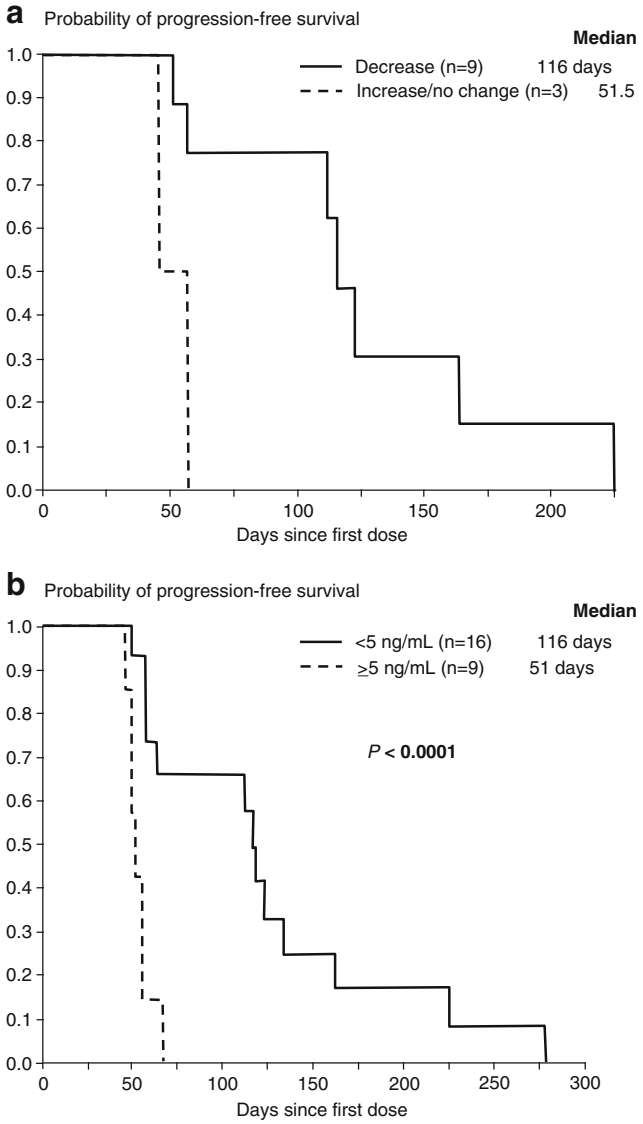

Fig. 3 Exploratory biomarkers. **a**, circulating tumor cells. **b** carcinoembryonic antigen (CEA)

better response in this population could not be assessed in this study.

This study is one of the first to evaluate the role of combination therapy targeting PARP-1 in patients with mCRPC. Based on the facts that androgen signaling in prostate cancer cells is directly coupled with the induction of DNA damage [41], CRPC tumor cells exhibit increased PARP-1 activity [15], veliparib improves the response to hormone therapy in preclinical prostate cancer models [15], PARP-1 is required for ERG-associated function and ERG:TMPRSS2-positive xenografts are sensitive to PARP inhibition [35], an ongoing clinical trial is currently assessing abiraterone acetate and prednisone with and without veliparib (administered at 300 mg BID days 1–28, a much higher dose than the present study) in patients with mCRPC. The primary objectives of the trial are to assess the role of ETS gene fusion as a predictive biomarker for response to hormone therapy alone or in combination with PARP-1 targeted therapy using veliparib, and whether the addition of PARP-1 targeted therapy is superior to hormone therapy alone based on ETS gene fusion status (ClinicalTrials.gov trial registration ID: NCT01576172).

Conclusion

This pilot study in chemotherapy-treated patients with mCRPC indicates that the combination of veliparib and TMZ is well tolerated, with evidence of modest antitumor activity. Low baseline concentrations of CEA and on-treatment decreases in CTC were associated with longer PFS. Evaluation of other combination therapies with higher doses of veliparib is warranted in this patient population.

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Disclosures AbbVie provided financial support for the study and participated in the design, study conduct, analysis and interpretation of data as well as the writing, review and approval of the manuscript.

Conflict of interest Jiang Qian, Evelyn McKeegan, Marion Refici-Buhr, Brenda Chyla. Stacie Shepherd and Vincent Giranda are employees and stock owners of AbbVie. Maha Hussain, Michael Carducci, Susan Slovin, Jeremy Cetnar, and Joshi Alumkal have no conflicts to disclose.

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Prostate Cancer

Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort

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Abstract

Background: Pain negatively affects quality of life for cancer patients. Preliminary data in metastatic castration-resistant prostate cancer (mCRPC) suggested a benefit of the oral tyrosine kinase inhibitor cabozantinib to pain palliation.
Objective: Prospective evaluation of cabozantinib's benefits on pain and narcotic use in mCRPC.
Design, setting, and participants: This was a nonrandomized expansion (NRE) cohort (n = 144) of a phase 2 randomized discontinuation trial in docetaxel-refractory mCRPC patients. Pain and interference of symptoms with sleep and general activity were electronically self-reported daily for 7-d intervals at baseline and regularly scheduled throughout the study. Mean per-patient scores were calculated for each interval. Narcotic use was recorded daily during the same intervals.
Intervention: Open-label cabozantinib (100 mg or 40 mg).
Outcome measurements and statistical analysis: The following stringent response definition was used: clinically meaningful pain reduction (≥30% improvement in mean scores from baseline) confirmed at a later interval without concomitant increases in narcotics. Only patients with moderate or severe baseline pain were analyzed.
Results and limitations: Sixty-five patients with moderate or severe baseline pain were evaluable. Of these, 27 (42%) experienced pain palliation according to the stringent

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response definition. Thirty-seven patients (57%) had clinically meaningful pain relief at two consecutive intervals, reported ≥6 wk apart in the majority. Forty-four patients (68%) had palliation at one or more intervals; 36 (55%) decreased narcotics use during one or more intervals. Clinically meaningful pain reduction was associated with significant ($p \leq 0.001$) improvements in sleep quality and general activity. A limitation of this study was its open-label design.

Conclusions: Cabozantinib demonstrated clinically meaningful pain palliation, reduced or eliminated patients' narcotic use, and improved patient functioning, thus meriting prospective validation in phase 3 studies.

Patient summary: We evaluated the potential of cabozantinib to improve symptoms in patients with metastatic prostate cancer that no longer responds to standard therapies. We saw a promising reduction in pain and reduced need for narcotic painkillers. Larger, well-controlled trials are necessary to confirm these findings.

1. Introduction

Most patients with advanced castration-resistant prostate cancer (CRPC) develop bone metastases frequently associated with debilitating pain that is, itself, associated with shorter survival [1]. For those with severe pain, symptoms are rarely eliminated despite optimal management with narcotic analgesics [2], which carry numerous side effects, thus reducing overall functioning even further. Anticancer treatments are needed in this disease that effectively control pain and enable reduction of narcotics.

The receptor tyrosine kinase MET and the vascular endothelial growth factor (VEGF) signaling pathway are implicated in development and progression of CRPC [3]. MET expression appears to be greater in bone metastases than primary tumors and lymph node metastases [4]; the VEGF pathway promotes bone lesion development and activates MET in advanced prostate cancer [3]. Cabozantinib is an orally bioavailable tyrosine kinase inhibitor of MET and VEGF receptor 2 that has demonstrated clinical activity in multiple types of solid tumors [5,6]. In a recent phase 2 randomized discontinuation trial (RDT) that enrolled 171 patients with metastatic CRPC (mCRPC), single-agent cabozantinib demonstrated increased progression-free survival compared with placebo, along with reductions in soft-tissue lesions, bone metastasis burden, and bone-turnover markers; common toxicities seen at the 100-mg dose in this population included fatigue, hand–foot syndrome, and diarrhea, which were typically manageable with either a dose reduction, treatment interruption, or supportive measures [7]. Randomization was halted early due to the clinical activity observed [7]. In a prospective, nonrandomized expansion (NRE) cohort of the phase 2 study, cabozantinib resulted in improvements on bone scans as well as reductions in bone biomarkers, soft-tissue disease, and circulating tumor cells [8,9].

Separately, a retrospective survey of participating investigators found widespread perceptions of pain benefits in the RDT. To explore this further, a formal prospective evaluation of pain using a rigorous measurement approach in accordance with relevant US Food and Drug Administration (FDA) guidance on patient-reported outcomes (PROs) [10,11] that met contemporary standards for pain assessment was needed [12,13]. Evaluating pain is no different from the development of other biomarkers, requiring analytically valid measurements and demonstrated clinical validity in appropriately designed and powered prospective trials. Studies of approved anticancer therapies in mCRPC have demonstrated modest pain palliation [14–16], but have not consistently evaluated PROs in line with current FDA guidance and contemporary methodology [13,17–21]. Supplemental Table 1 provides an overview of these requirements.

Since pain palliation is a stand-alone primary end point for which therapies have been approved in this disease, we explored whether the pain benefit observed in the RDT was sufficient to warrant the design of a phase 3 registration trial in mCRPC with a dedicated pain end point. To this end, we applied contemporary pain assessment methodology to the NRE cohort [13,22], exploring changes in pain, interference of symptoms with patients' daily living, and narcotic analgesia use.

2. Patients and methods

The patients described in this report were from the NRE cohort of the fully enrolled, phase 2 RDT XL184-203 [7]. Patients with progressive mCRPC (according to standard, objective criteria [23,24]) during treatment with a taxane- or abiraterone-containing regimen (or within 6 mo following the last dose), evidence of bone metastasis on bone scans, and previous docetaxel treatment were sequentially enrolled to two starting doses of open-label cabozantinib, first 100 mg then 40 mg daily, as part of a dose-ranging evaluation. Patients taking prednisone ≤10 mg/d were eligible for enrollment. The study design is described in detail elsewhere [22] and in the Supplement.

The study was approved by all local institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The trial is registered at ClinicalTrials.gov (identifier: NCT00940225).

Once daily, patients were to self-report pain and interference of symptoms with daily living, using an automated, telephone, interactive voice-response system (IVRS), over 7-d intervals at screening (within 14 d before the first dose), at week 3, week 6, and every 6 wk thereafter, using select items from the Brief Pain Inventory short form (BPI-SF) and MD Anderson Symptom Assessment Inventory (MDASI) questionnaires [25,26]. Pain assessments were halted at patient request or if patients discontinued study treatment other than for progression. During each interval, patients reported their worst pain in the prior 24 h (item 3 on the BPI-SF) and the interference of cancer symptoms with sleep and general activity over the same period (items 4 and 14, respectively, on the MDASI). All three items use a 0–10 numeric rating scale, with higher scores representing greater pain intensity or symptom interference.

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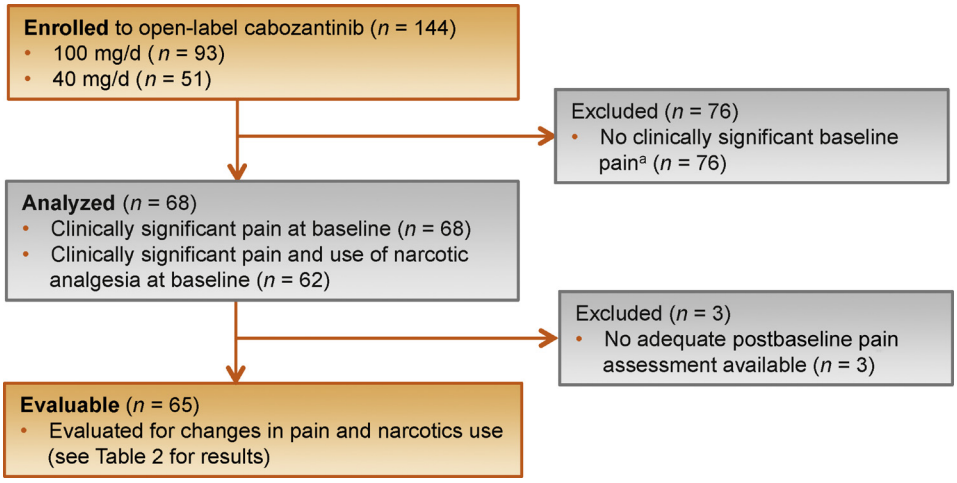

Fig. 1 – Flowchart of patient enrollment and pain analyses in the nonrandomized expansion metastatic castration-resistant prostate cancer cohort.
[a] Mean score of the "worst pain reported over 24 h" item of the Brief Pain Inventory Short Form questionnaire over the 7-d baseline reporting interval (scores for at least 4 d had to be reported) was <4.

Patients reported daily analgesic medication use via a paper diary during the same assessment intervals in which pain scores were measured. Prior to each interval, clinical research nurses prepopulated the diary of each participant with the names and dosages of the narcotic medications prescribed, so that patients merely had to indicate the number of doses taken by the end of each 24-h period. This approach closely follows current regulatory recommendations [13]. For each interval, patients' mean narcotics use was calculated by multiplying the daily dose unit by the number of units taken, averaged by the number of days with available data. Changes in narcotic use were qualified as decreased (including discontinued), stable, or increased, based on the average daily narcotics use relative to the baseline interval. Narcotics use was considered stable if the average daily dose of a given narcotic was identical. Equianalgesia calculations [27] were required to quantify narcotic use if patients changed narcotic type or if dosages were changed in patients concomitantly receiving different narcotic types. In cases where equianalgesia calculations were required, narcotics use was considered stable if the calculated equivalents were within 5% of the baseline dose.

Mean scores for pain, disturbed sleep, and interference with general activity were calculated over each 7-d interval. For an interval to be considered evaluable for analysis of a specific measure (including analgesic use), reporting on ≥4 d out of 7 was required. Only patients with a baseline, mean worst pain score ≥4, corresponding to moderate or severe pain using a verbal analog scale [28], and one or more evaluable follow-up assessments were included in the analyses. A decrease in the mean worst pain score ≥30% from baseline was prospectively defined as clinically meaningful improvement based on standard definitions [20,21]. The pain response definition used for the main analysis was the currently recommended [10,13,24], more conservative measure, requiring a clinically meaningful improvement that is confirmed at a later time point without a concurrent increase in narcotics use. There was no prespecified decision rule as to the proportion of patients experiencing a response to inform the decision to further study cabozantinib for a pain relief indication.

A decrease in the mean sleep disturbance or mean symptom interference scores (determined over the same 7-d interval as the mean worst pain score) from baseline corresponded to an improvement in sleep or functioning, respectively. Differences in measures of symptom interference between patients with and without clinically meaningful pain palliation were assessed by the Mann-Whitney test.

3. Results

A total of 144 mCRPC patients were enrolled to the NRE cohort at 13 sites in the United States and one in the United Kingdom between February 2011 and April 2012. Patients were enrolled sequentially to two starting doses of open-label cabozantinib: first 100 mg daily ($n = 93$) then 40 mg daily ($n = 51$). Main results, including details on dose reductions, are presented in detail elsewhere [22].

A total of 68 patients (47%) who reported moderate or severe pain at baseline constituted the population for this analysis, of whom 62 also reported baseline narcotic analgesia use (Fig. 1). The median baseline pain score was 5.9 (range: 4.0–7.9; lower and upper quartiles: 4.7 and 6.7, respectively). Additional baseline characteristics for the analysis population are listed in Table 1. Of note, in addition to prior docetaxel, patients were heavily pretreated with

Table 1 – Characteristics of patients with baseline pain score ≥4 (*n* = 68)

Age, yr, median (lower quartile, upper quartile)	64 (57, 70)
ECOG performance status, no. (%)[a]	
0	17 (25)
1	50 (74)
Bone disease, no. (%)	68 (100)
At least two prior regimens for mCRPC, no. (%)	52 (76)
Prior treatment, no. (%)	
Docetaxel	68 (100)
Abiraterone	34 (50)
Cabazitaxel	16 (24)
Enzalutamide	2 (3)
Radionuclide	7 (10)
Use of bone-targeted therapy[b], no. (%)	44 (65)

ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer.
[a] One patient was enrolled with an ECOG performance status of 2.
[b] Zoledronic acid or denosumab at baseline (includes one patient who discontinued zoledronic acid within 60 d prior to first dose of cabozantinib).

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Table 2 – Effects of cabozantinib on mean worst pain and narcotic use

	Cabozantinib cohort		
	100 mg	40 mg	Combined
Pain ≥4 at baseline[a], no.	39	26	65
Pain reduction ≥30% at any time point, no. (%) [95% CI]	25 (64) [47–79]	19 (73) [52–88]	44 (68) [55–79]
Pain reduction ≥30% at two or more consecutive assessments[b], no. (%) [95% CI]	22 (56) [40–72]	15 (58) [37–77]	37 (57) [44–69]
Pain reduction ≥30% at two or more consecutive assessments[b] with no concomitant increase in narcotics[c], no. (%) [95% CI]	15 (38) [23–55]	12 (46) [27–67]	27 (42) [29–54]
Median best change in pain, % reduction	46	49	46
Decreased narcotics at any time point[d], no. (%) [95% CI]	22 (56) [40–72]	14 (54) [33–73]	36 (55) [43–68]
Decreased narcotics at two or more consecutive assessments[e], no. (%) [95% CI]	21 (54) [37–70]	13 (50) [30–70]	34 (52) [40–65]

Data are shown for the 65 patients with pain score ≥4 at baseline who had at least one adequate postbaseline pain assessment. Equianalgesia calculations were used to determine changes in narcotic use for patients who modified narcotics types throughout the assessments.
[a] Patients with at least one adequate postbaseline pain assessment, denominator for percent calculations.
[b] Includes eight patients whose consecutive assessments were at week 3 and week 6; for the remaining patients, the two consecutive assessments were at least 6 wk apart.
[c] Includes patients who did not take any narcotics at baseline and did not add any narcotics, as well as patients who stayed on the same dose of narcotics at baseline and the two consecutive assessments.
[d] Includes patients who discontinued narcotics at any time point (100 mg [$n = 12$]; 40 mg [$n = 1$]).
[e] Includes patients who discontinued narcotics at two consecutive time points (100 mg [$n = 9$]; 40 mg [$n = 1$]).

other medications for mCRPC, including abiraterone (50% of patients), cabazitaxel (24%), and enzalutamide (3%). Overall, 76% of patients had received two or more prior regimens (including docetaxel) for mCRPC. Patients readily complied with the IVRS reporting: In the analysis population, a total of 292 IVRS reporting intervals were administered (through week 18) prior to treatment discontinuation, and 93% of these intervals were evaluable (ie, patients reported pain on ≥4 d out of 7 for the respective interval).

Pain and narcotic use were evaluable for 65 of the 68 patients and are summarized in Table 2, categorized by dose group (100 mg, $n = 39$;40 mg, $n = 26$). Overall, 27 of the 65 patients (42%) reported a clinically meaningful improvement (≥30% decrease) in the mean worst pain score at two consecutive assessments without a concomitant increase in narcotic use (Table 2), representing a conservative definition of durable pain palliation according to Prostate Cancer Working Group 2 (PCWG2) criteria and other current guidance [10,13,24]. Additional analyses showed that 44 patients (68%) had one or more postbaseline assessments with a clinically meaningful improvement (Fig. 2A); median change in pain score was a 46% reduction that was confirmed at a subsequent assessment in 37 patients (57%) (Table 2).

Of those with evaluable data at week 6 ($n = 61$) and week 12 ($n = 49$), 57% and 53%, respectively, reported a clinically meaningful decrease in the mean worst pain score (Fig. 2B and 2C). The median change in mean worst pain score was below baseline for each time point (Fig. 3): −22% (week 3), −38% (week 6), −31% (week 12), and −36% (week 18). In the majority of patients (76–84%, depending on the specific time point) with concomitant narcotics reporting, clinically meaningful reductions in pain were not associated with increased narcotics use (Fig. 2A–2C; Table 2). Pain palliation effects were similar in the 40-mg and 100-mg cohorts (Fig. 2A–2C; Table 2).

Thirty-six of the 65 evaluable patients (55%) reported a decrease in narcotic use during one or more postbaseline intervals, including 13 (20%) who discontinued narcotics during that period. Proportions of patients who decreased narcotics at any time point were comparable between both dose groups (Table 2). Overall, 34 patients (52%) decreased narcotics at two or more consecutive assessments. At each time point, the majority of patients reported either decreased or stable narcotics (Fig. 4).

The relationships between clinically meaningful pain palliation and both sleep disturbance and general activity were assessed at matching time intervals. At each of these time points, patients with pain palliation were significantly more likely to experience improvements in sleep quality and interference with general activity than patients without pain palliation. Figure 5A illustrates that improvements in disturbed sleep differed significantly between those who experienced a ≥30% reduction in pain and those who did not, with median changes of −53% versus 1% at week 3, −47% versus −4% at week 6, −41% versus 5% at week 12, and −56% versus −9% at week 18 ($p < 0.0001$ for each time interval). As shown in Figure 5B, improvements in functioning differed significantly between those who experienced a ≥30% reduction in pain and those who did not, with median changes of −32% versus 0% at week 3 ($p = 0.0006$), −43% versus −3% at week 6 ($p < 0.0001$), −42% versus 8% at week 12 ($p < 0.0001$), and −32% versus 14% at week 18 ($p = 0.001$).

4. Discussion

By rigorous contemporary assessment standards, cabozantinib demonstrated pain palliation in heavily pretreated men with symptomatic mCRPC in this phase 2 NRE cohort. Overall, 42% of evaluable patients reported clinically meaningful improvement in worst pain confirmed at a

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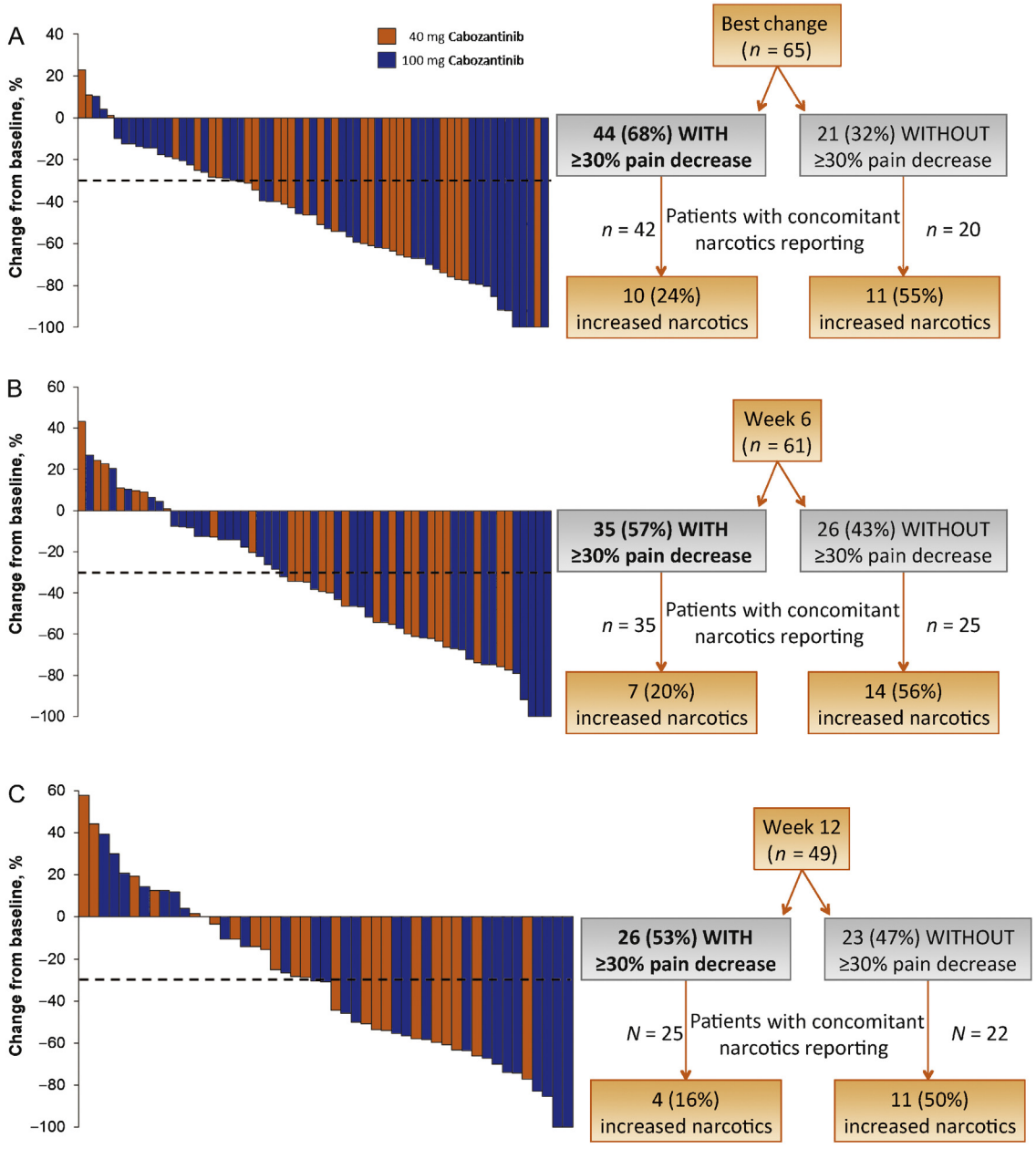

Fig. 2 – Change from baseline in mean worst pain and associated narcotics changes. Starting doses of cabozantinib were 100 mg and 40 mg. (A) Best change. Data are shown for the 65 patients with pain score ≥4 at baseline who had a least one adequate postbaseline pain assessment. The dashed line denotes a 30% improvement in mean worst pain score. (B) Data are shown for the 61 patients with pain score ≥4 at baseline and adequate pain reporting at week 6. (C) Data are shown for the 49 patients with pain score ≥4 at baseline and adequate pain reporting at week 12.

second assessment without concomitant increases in narcotics use, a conservative definition of pain palliation in cancer trials [10,13,24]. More than two-thirds of patients experienced one or more assessment intervals with clinically meaningful pain improvement, enabling 20% of patients to discontinue narcotic usage. The global impact of pain palliation on overall patient well-being was shown by parallel improvements in sleep and daily function.

Preclinical models of prostate cancer indicate that cabozantinib targets prostate cancer cells as well as cells of the bone microenvironment (including osteoblasts and osteoclasts), inhibiting tumor growth and tumor-induced bone changes [29,30]. The impact of cabozantinib on pain due to bone metastases may be related to its effects on both cancer cells and the surrounding bone microenvironment.

Pain palliation appeared as early as week 3, when 39% of patients with evaluable data reported clinically meaningful pain reduction, and increased to 57% at week 6. Overall, 57% of evaluable patients reported improvement at two consecutive assessment intervals. Pain outcomes were similar for the 40-mg and 100-mg starting-dose groups. Of note, cabozantinib dose-reduction rates were similar to those in the overall NRE cohort, in which 84% of patients enrolled to the 100-mg cohort had one or more dose

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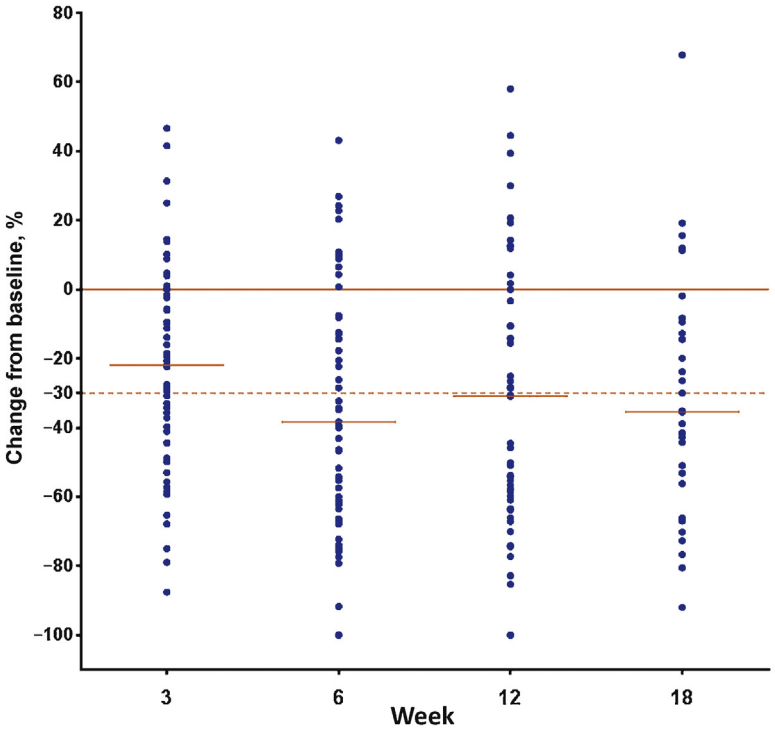

	Week 3	Week 6	Week 12	Week 18
Patients evaluable, no.	61	61	49	31
Median change in pain score, %	−22	−38	−31	−36
Pain reduction ≥30%, no. (%)	24 (39)	35 (57)	26 (53)	18 (58)

Fig. 3 – Changes in mean worst pain over time. Data are shown for patients with pain score ≥4 at baseline with ≥4 of 7 d reported during each postbaseline interval. The dashed line denotes a 30% improvement in mean worst pain.

reductions [22]. The outcomes for the 100-mg and 40-mg cohorts are not directly comparable, because the study was not randomized and due to the relatively small patient number per cohort. Moreover, due to protocol-specified dose modifications in the overall NRE population, the median average daily dose in the 100-mg cohort was actually 55 mg/d, minimizing the difference in actual dose administered between cohorts; based on these results, 60 mg/d was selected as the starting dose for subsequent phase 3 trials [22].

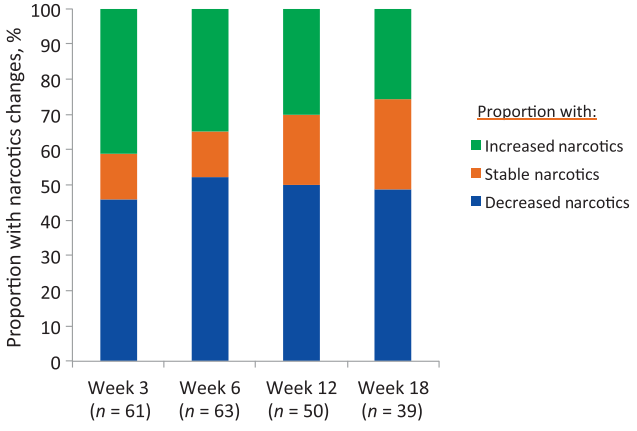

Fig. 4 – Proportion of patients with narcotics changes over time. The proportion of patients with changes in narcotic use is shown for patients with pain score ≥4 at baseline and available diary data at each time point.

For historical comparison, in a recent phase 3 trial in docetaxel-refractory mCRPC patients, 7.7% of mitoxantrone-treated patients showed a pain response; mitoxantrone remains the only chemotherapeutic agent with a pain palliation FDA-labeling claim in mCRPC. That trial used a different pain scale than our study, but similarly used repeated pain assessments over 7 d self-reported by IVRS, and incorporated analgesic use and the requirement for a confirmatory response at a second time point [16].

At baseline, >90% of our patients with moderate or severe pain received narcotic analgesics, which is not surprising given their pain levels and the fact that all patients were managed by oncologists specializing in caring for prostate cancer patients. This rate is higher than reported in large, community-based cohort studies, which have suggested underuse of narcotics in cancer patients [31]. This high prevalence of narcotic use provides valuable

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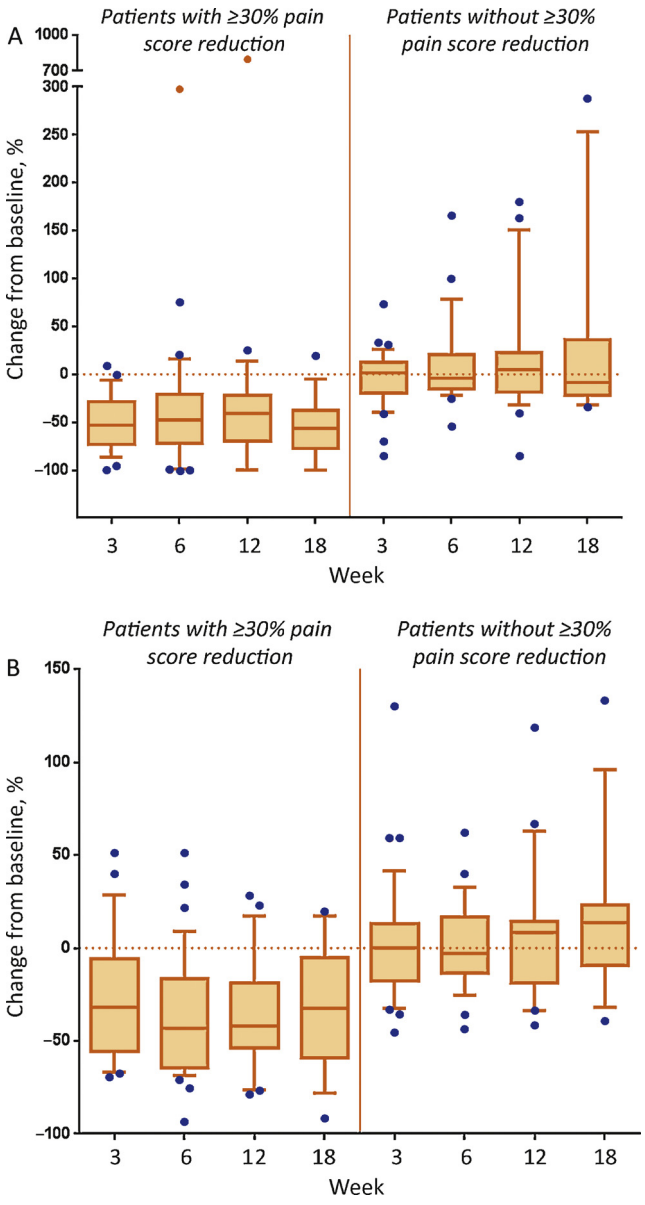

Fig. 5 – Relationship of pain with sleep disturbance and functioning over time. (A) Percent change from baseline in disturbed sleep score in patients with or without clinically meaningful pain score reduction. (B) Percent change from baseline in symptom interference score (interference with general activity) in patients with or without clinically meaningful pain score reduction.

insight into the palliative benefit of cabozantinib, since >50% of evaluable patients were able to decrease these medications. The ability to reduce narcotics may have the additional benefit of alleviating the side effects associated with these agents; ongoing trials of cabozantinib are formally evaluating this topic.

The prevalence of moderate or severe baseline pain was similar to that reported in recent phase 3 studies among mCRPC patients who experienced disease progression despite prior docetaxel therapy (28–46%) [14,16,32]. Like other PROs in clinical trials, methods for evaluating pain have evolved over time, and previous studies generally used less rigorous methods for assessing pain and analgesic usage. Our study used a rigorous contemporary methodology to critically evaluate pain.

Key elements of contemporary pain studies in oncology include the use of validated PRO measures for a particular population, repeated measurements to obtain an average score, meaningful intervals that can also assess the durability of response, and incorporation of analgesic use into responder definitions [13]. Our study fulfilled these criteria. The BPI instrument, in particular the worst pain item assessing the prior 24 h, has well-established psychometric properties that meet FDA guidelines for PRO end point measures [10,11,33]. The repeated daily assessments over 7-d intervals used to determine an average score are preferred over single scores, which may be more susceptible to random day-to-day variation. A priori definition of a clinically meaningful difference for all evaluated PRO measures is another important principle. In the case of patient-reported pain, a ≥30% change from baseline is widely accepted as such a meaningful difference [20]. While the data from this NRE cohort suggest a promising palliative response with cabozantinib, direct comparisons with other agents cannot be made, due to differences in study design, patient populations, and sample sizes of relevant published clinical trials.

A key to conducting successful pain palliation trials is close coordination between the treating team and their patients. Notable here is that compliance with PRO reporting was high, with 93% of relevant assessment intervals (through week 18) completed adequately. This may be attributable partially to the IVRS system and automated, real-time assessments (with reminders) that are convenient to use for patients and investigators. Adequate compliance is essential for trials reporting PRO measures, since noncompliance could be reflective of worsening symptomatology.

This open-label, nonrandomized, phase 2 design is not definitive, due to possible bias in PRO reporting associated with unblinded assessments. The study design precluded any meaningful analysis of associations between pain control and markers of disease progression. The degree of palliation observed resulted in the decision to design a prospective, phase 3, double-blind, randomized trial of cabozantinib with a primary end point of pain palliation. Lack of an analgesic optimization phase prior to study entry, which could potentially have altered results, is a limitation of the current study. However, patients received narcotics with much greater frequency than in community-based samples among populations with similar pain severity [31], suggesting that some of the obstacles to analgesic use (eg, physician failure to recognize pain and patient concerns for addiction) were being well-managed in this patient cohort.

Taken together, the results reported here, which are based on contemporary methods and regulatory guidance for PRO assessment, found pain palliation rates were well in excess of those seen in control arms of registration trials in mCRPC, many of which used prednisone in the control arm, rather than placebo. Prednisone is an active agent in this context, with reported pain palliation at stable or reduced

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analgesic consumption reported in 12–29% of patients [14,15]. Since the pain palliation signal and the reductions in narcotic use observed with cabozantinib substantially exceed these previously reported levels, an effect beyond placebo is likely and justifies the design and conduct of a dedicated pain palliation phase 3 trial towards a formal indication [16,34].

5. Conclusions

Pain palliation remains a critical unmet need in treating patients with mCRPC. According to PCWG2 recommendations, relief or elimination of disease-related symptoms is a clinical benefit of prostate cancer therapy [22], with pain palliation being a clinical benefit that is an approvable end point in its own right [13]. Our results illustrate that contemporary pain palliation trials [11], while challenging to conduct, are feasible and can generate valuable information about symptoms as directly reported by patients. This phase 2 NRE cohort implemented key elements desired from a modern pain trial and thus provided justification for, as well as informed the study design of, the blinded, randomized, phase 3 COMET-2 trial; ClinicalTrials.gov identifier NCT01522443). That trial will further assess the promising pain response observed with cabozantinib as the primary end point, as well as evaluate whether pain improvement is reflective of disease regression or stabilization. In that trial, which includes mitoxantrone plus prednisone as an active control, a similar conservative definition of pain palliation at two consecutive time points with no increase in narcotics is the primary efficacy outcome. The present analysis, analogous to a phase 2 signal-seeking study, was an essential step in the clinical qualification process prior to conducting a randomized, controlled, phase 3 trial. This step-wise approach reflects the rigorous methodology that is needed to ultimately validate and potentially qualify a biomarker (ie, pain palliation). For future trials evaluating therapies for advanced cancer, investigators are encouraged to implement patient-reported measures to fully elucidate the potential clinically meaningful benefits of novel antitumor agents.

Author contributions: Ethan M. Basch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Basch, MR Smith, Bennett, Weitzman, Scheffold, Sweeney, Rathkopf, DC Smith, George, Higano, Harzstark, Sartor, Gordon, Vogelzang, de Bono, Haas, Corn, Scher.
Analysis and interpretation of data: Basch, Autio, MR Smith, Bennett, Weitzman, Scheffold, Sweeney, Sartor, Vogelzang, Corn, Schimmoller, Scher.
Drafting of the manuscript: Basch, Autio, Bennett, Scher.
Critical revision of the manuscript for important intellectual content: Basch, Autio, MR Smith, Bennett, Weitzman, Scheffold, Sweeney, Rathkopf, DC Smith, George, Higano, Harzstark, Sartor, Gordon, Vogelzang, de Bono, Haas, Corn, Schimmoller, Scher.
Statistical analysis: Basch, Bennett, Schimmoller.
Obtaining funding: Weitzman.
Administrative, technical, or material support: Scheffold, Schimmoller.
Supervision: Basch, Weitzman.
Other (specify): None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.02.013.

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PHASE II STUDIES

A randomized phase II study of cediranib alone versus cediranib in combination with dasatinib in docetaxel resistant, castration resistant prostate cancer patients

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Summary *Background* Activation of the vascular endothelial growth factor receptor (VEGFR) and the oncogenic Src pathway has been implicated in the development of castration-resistant prostate cancer (CRPC) in preclinical models. Cediranib and dasatinib are multi-kinase inhibitors targeting VEGFR and Src respectively. Phase II studies of cediranib and dasatinib in CRPC have shown single agent activity. *Methods* Docetaxel-pretreated CRPC patients were randomized to arm A: cediranib alone (20 mg/day) versus arm B: cediranib (20 mg/day) plus dasatinib (100 mg/day) given orally on 4-week cycles. Primary endpoint was 12-week progression-free survival (PFS) as per the Prostate Cancer Clinical Trials Working Group (PCWG2). Patient reported outcomes were evaluated using Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Present Pain Intensity (PPI) scales. Correlative studies of bone turnover markers (BTM), including bone alkaline phosphate (BAP) and serum beta-C telopeptide (B-CTx) were serially assayed. *Results* A total of 22 patients, 11 per arm, were enrolled. Baseline demographics were similar in both arms. Median number of cycles =4 in arm A (range 1–12) and 2 in arm B (range 1–9). Twelve-week PFS was 73 % in arm A versus 18 % in arm B (p=0.03). Median PFS in months (arm A versus B) was: 5.2 versus 2.6 (95 % CI: 1.9–6.5 versus 1.4-not reached). Most common grade 3 toxicities were hypertension, anemia and thrombocytopenia in arm A and hypertension, diarrhea and fatigue in arm B. One treatment-related death (retroperitoneal hemorrhage) was seen in arm A. FACT-P and PPI scores did not significantly change in either arm. No correlation between BTM and PFS was seen in either arm. *Conclusions* Although limited by small numbers, this randomized study showed that the combination of VEGFR and Src targeted therapy did not result in improved efficacy and may be associated with a worse outcome than VEGFR targeted therapy alone in patients with CRPC. ClinicalTrials.gov number: NCT01260688.

Keywords Cediranib · Dasatinib · Castration resistant prostate cancer · Quality of life · Bone turnover marker

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Introduction

Over the last few years, treatment options for patients with castration-resistant prostate cancer (CRPC) have evolved from older generation antiandrogens and chemotherapy to now include novel androgen receptor signaling inhibitors, next-generation taxanes, as well as immunotherapy. Docetaxel, cabazitaxel, enzalutamide, abiraterone acetate, radium-223 and sipuleucel-T have all been associated with improved overall survival in randomized clinical trials in metastatic CRPC patients [1–9]. Despite the approval of these novel agents, resistance is inevitable and new treatment approaches are needed, highlighting the impact of new drug development in the cancer setting.

Preclinical data have demonstrated that the Vascular Endothelial Growth Factor (VEGF) and the proto-oncogene tyrosine-protein kinase Src may play a crucial role in the development and progression of prostate cancer [10–14], both through a Src-related activation of the MAPK, PI3K/AKT/mTOR and STAT3 signaling pathways [15, 16] and direct hormonal control of angiogenesis in the early stages of prostate carcinogenesis [17, 18]. Importantly, VEGF and Src have been shown to be instrumental in osteoclast function and bone formation [19–22]. In particular, osteoclast and osteoblast proliferation and consequent bone remodeling has been associated with alteration of mineral homeostasis and bone architecture through the effects of several cytokines, such as VEGF, generated by tumor cells. [23, 24]. Additionally, expression of Src induces rearrangements of the actin cytoskeleton and regulates the structure and organization of podosomes, actin-rich protrusions, which coordinate extracellular matrix degradation with cell motility, to facilitate normal cell migration through tissue microenvironments [19]. Furthermore, previous data have shown a proangiogenic role of Src through hypoxia-driven VEGF induction [16, 25]. Previous in vivo studies have shown statistically significant tumor growth inhibition with cediranib, a VEGF receptor inhibitor, in combination with saracatinib, a dual-specific inhibitor of Src and Abl, as compared to treatment with either single agent alone in lung cancer xenograft models [26]. In the phase I setting, the combination of saracatinib and cediranib was well tolerated and demonstrated disease control [27, 28]. Therefore, targeting both angiogenesis and Src appears to be a rational therapeutic strategy for patients with advanced prostate cancer.

Cediranib (AZD2171 maleate, Recentin™; AstraZeneca) is an orally available, potent inhibitor of VEGF receptor tyrosine kinases (RTKs) -1, −2 and −3, and has also shown activity against c-kit and platelet-derived growth factor receptors (PDGFR) with effects on cell migration and invasion [29–31]. In preclinical models of prostate cancer expressing PDGF-D, previously shown to have an oncogenic activity in prostate cancer progression and to be associated with tumor stage and Gleason grade [32, 33], cediranib has exhibited intraosseous growth reduction [34]. In the clinical setting, cediranib has been safely administrated both as a single agent and in combination with either platinum-based chemotherapy or other targeted agents in patients with advanced cancer, and has demonstrated modest clinical benefit in specific tumor types such as prostate and renal cell cancer [35–42]. Recent results from a randomized, double-blind phase III study have shown that cediranib both in combination with concurrent platinum-based chemotherapy as well as maintenance post chemotherapy, increased PFS and OS in patients with recurrent ovarian carcinoma [43]. Additional studies are evaluating the safety, tolerability and efficacy of cediranib in several tumor types (clinicaltrials.gov).

Dasatinib (SPRYCEL; Bristol-Myers Squibb) is an oral protein tyrosine kinase (PTK) inhibitor with specificity for BCR-ABL, c-Src, c-kit, PDGFRβ, and EPHA2 [44]. It is currently indicated for the treatment of chronic phase (CP) Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) [45, 46]. In the preclinical setting, dasatinib has shown decreased cellular proliferation, migration, and invasion in prostate cancer tumor cells, as well as inhibition of tumor growth and lymph node metastases in both androgen-sensitive and androgen-resistant orthotopic nude mouse models, resulting in inhibition of activated Src Family Kinases (SFKs) expression [47, 48]. Additionally, dasatinib has been shown to reduce osteoclast activity [49, 50]. In the prostate cancer setting, dasatinib has been investigated in several phase I and II clinical trials both as a single agent and in combination with chemotherapy or other targeted therapies, with variable results with regards to tolerability and efficacy but with promising bone activity with reduction or normalization of markers of bone metabolism such as urinary N-telopeptide and bone alkaline phosphatase (BAP) and stabilization of bone metastases [51–55].

The combination of cediranib and another Src inhibitor, saracatinib, (AZD0530; AstraZeneca) has been tested in a phase I clinical trial of patients with advanced solid tumors [27]. In this study, the combination exhibited a favorable toxicity profile with hypertension as the most common adverse event and promising preliminary evidence of efficacy with stable disease, as per RECIST version 1, observed in 22 out of 35 (63 %) evaluable patients [27].

The purpose of this randomized phase II clinical trial was to evaluate the clinical activity of cediranib with or without dasatinib in CRPC patients whose disease had progressed on first-line docetaxel-based chemotherapy.

Materials and methods

Study objectives

The primary objective of this study was to determine and compare the efficacy of cediranib versus cediranib and

dasatinib in patients with metastatic CRPC utilizing progression free survival (PFS) as per the Prostate Cancer Clinical Trials Working Group (PCWG2), which includes a compilation of prostate-specific antigen (PSA), bone scan, and CT-scan assessments [56]. The secondary objectives were: safety and tolerability confirmation as well as objective response rate analysis of cediranib with or without dasatinib; symptom assessment using the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire [57] and the present pain intensity (PPI) scale from the McGill-Melzack questionnaire [58], and correlative biomarkers analysis, such as evaluation of bone turnover markers, including beta C-telopeptide (β-CTX) and bone-specific alkaline phosphatase (BAP) . Full protocol is available in Appendix 1 of supplementary material.

Patients and eligibility criteria

Eligible patients included men with castration-resistant, histologically confirmed prostate cancer previously treated with docetaxel and who had a European Cooperative Oncology Group Performance Status (ECOG PS)≤2, estimated life expectancy greater than 3 months, and adequate marrow and organ functions [absolute neutrophil count≥1.5×10^9/L; Hb> 90 g/L; Platelets≥100×10^9/L; INR ≤1.3; Total bilirubin ≤1.25 × institutional upper limit of normal (ULN); AST (SGOT) / ALT (SGPT) ≤2 × ULN or<5 × ULN if clearly attributable to liver metastasis; Creatinine≤ULN and calculated creatinine clearance (≥60 mL/min/1.73 m^2 for patients with creatinine level above institutional normal); urine dipstick for protein of less than +1; for dipsticks of +1 or more, 24-h urine collection for protein is necessary and should be <1 g/24 h]. Following docetaxel, patients may have had any number of chemotherapy regimens. Prior surgery, radiotherapy, radioisotopes, hormonal therapy, and targeted therapies other than angiogenesis, Src or FAK inhibitors were allowed upon appropriate washout period (3 to 4 weeks depending on the treatment). Presence of measurable, or non-measurable metastatic disease as defined by RECIST 1.0 [59], and clinical and/or radiological confirmation of disease progression on or after docetaxel treatment were mandatory. Patients with elevation of PSA alone without radiographic evidence of measurable or non-measurable disease were not eligible.

Study design, treatment and evaluation of clinical activity

This randomized, multicenter, phase II study was supported by the US National Cancer Institute, and approved by each center's Institutional Review Board and all patients provided written informed consent.

At baseline, all patients underwent history and physical examination, blood evaluation and appropriate diagnostic imaging. To assess Quality of Life (QoL), patients also completed both FACT-P and PPI questionnaires [57, 58]. Upon registration, patients were randomized to receive either single agent oral cediranib at 20 mg once daily or cediranib 20 mg once daily in combination with oral dasatinib at 100 mg once daily, continuously on a 28-day cycle. Treatment response, according to RECIST, was evaluated every 12 weeks [59]. Best overall response was defined as the best response recorded from the start of the treatment until disease progression/ recurrence. PPI and FACT-P questionnaires were undertaken at the beginning of each cycle. A reduction of at least 2 points in the PPI total score or 50 % in analgesic use from baseline and an improvement of 10 % (a sustained 16-point or greater improvement from baseline on consecutive measurements) in the FACT-P total score defined treatment-related pain and QoL response [60].

Bone turnover biomarkers

As a secondary objective, plasma bone turnover markers (BTM) beta C-telopeptide (β-CTX) and bone-specific alkaline phosphatase (BAP) were evaluated at baseline as well as at the end of cycles 1 and 3, using Elecsys β-crossLaps immunoassay (Roche Diagnostic, Indianapolis, IN) and Access Ostase immunoassay (Beckman Coulter, Brea CA) respectively, according to manufacturers' procedures. β-CTX is a specific resorption marker of degradation of bone type I collagen by osteoclasts, while BAP is a bone formation marker reflecting osteoblast activation. Our hypothesis was that β-CTX would decrease, while BAP would increase as a result of treatment in both arms, with a more pronounced effect when cediranib was given in combination with dasatinib.

Sequencing analysis

Tumor DNA, isolated from formalin-fixed paraffin-embedded (FFPE) archived samples, was characterized by Next Generation Sequencing (NGS) using either a customized Sequenom panel (PMH version 1.0, 23 genes, 279 mutations) on the Sequenom MassARRAY platform, or the commercially available Illumina MiSeq TruSeq Amplicon Cancer Panel (version 2.0, 48 genes, 212 amplicons, ≥500× coverage) on the Illumina MiSeq personal genome sequencer. Selected FFPE samples with insufficient DNA quantity to perform MiSeq analysis were genotyped using the Sequenom platform. All the analyses were performed in the Clinical Laboratory Improvement Amendments (CLIA)-certified University Health Network (UHN) Advanced Molecular Diagnostics Laboratory (AMDL).

Statistical analysis

Initially, this randomized phase II study aimed to enroll a total of 50 patients (25 patients per arm) to demonstrate a 30 % absolute improvement in the proportion of patients who were

progression-free at 12 weeks in the combination group as compared to single agent cediranib (estimating an improvement from 30 to 60 %). Unfortunately the study was closed prematurely due to discontinued supply of cediranib. Fisher's Exact test was used to compare the 12-week PFS proportions between the two treatment arms. Descriptive statistics were used for other aspects of the trial.

Results

Patients data

Between October 2010 and July 2012, 22 men with CRPC, 11 per arm, were recruited in seven centers of the three participating Consortia (Fig. 1). All patients were included in the analysis for 12-week PFS as per PCWG2. Patient characteristics were similar across the two treatment arms (Table 1) with most having a good ECOG performance status. Approximately half of the patients had target lesions (55 % in arm A and 45 % on arm B). Baseline pain, assessed by a score≥2 on the PPI scale, appeared to be slightly more prominent in patients enrolled in the combination arm.

Treatment administration

At the time of the data cut-off for final analysis (April 2013), all patients had completed treatment. In patients treated with cediranib alone (arm A), a total of 51 cycles with a median of 4 cycles (range, 1 to 12) were delivered, compared to a total of 31 cycles, with a median of 2 cycles (range, 1 to 9 cycles) for patients treated in the cediranib/dasatinib combination arm (arm B). During cycle 1, most of the patients in arm A (81 %) received cediranib at a dose intensity of over 80 % compared to the combination group (cediranib: 54 %, dasatinib 64 %). A similar trend was maintained in the subsequent cycles. The most common reasons of treatment discontinuation, which occurred in 55 % of patients in arm A and in 64 % of patients in arm B, were either progression of disease or consent withdrawal. One patient in arm A and two patients in arm B discontinued treatment because of adverse events (Fig. 1). After treatment discontinuation, 63 % of the patients enrolled in arm A underwent additional treatment (chemotherapy: 5 patients, radiotherapy: 2 patients), while 27 % of the patients treated with the combination study (arm B) received further therapy (chemotherapy: 1 patient, surgery: 2 patients).

Safety

The entire patient population enrolled in this study (n= 22) was evaluable for safety profile. The majority of the adverse events were considered mild or moderate and clinically manageable as summarized in Table 2. The most common drug-related adverse events of all grades in both arms were diarrhea, fatigue, hypertension, and nausea. In arm A, drug-related severe (grade≥3) adverse events included hypertension, anemia and thrombocytopenia, all seen in 27 % of patients, and retroperitoneal hemorrhage (grade 5), which occurred in one patient. In arm B severe adverse events included diarrhea and hypertension, described in 27 % of patients, fatigue, and lower and upper gastrointestinal hemorrhage (all grade 3), which occurred in 18 % of patients. The grade 5 drug-related hemorrhagic event that occurred in arm A

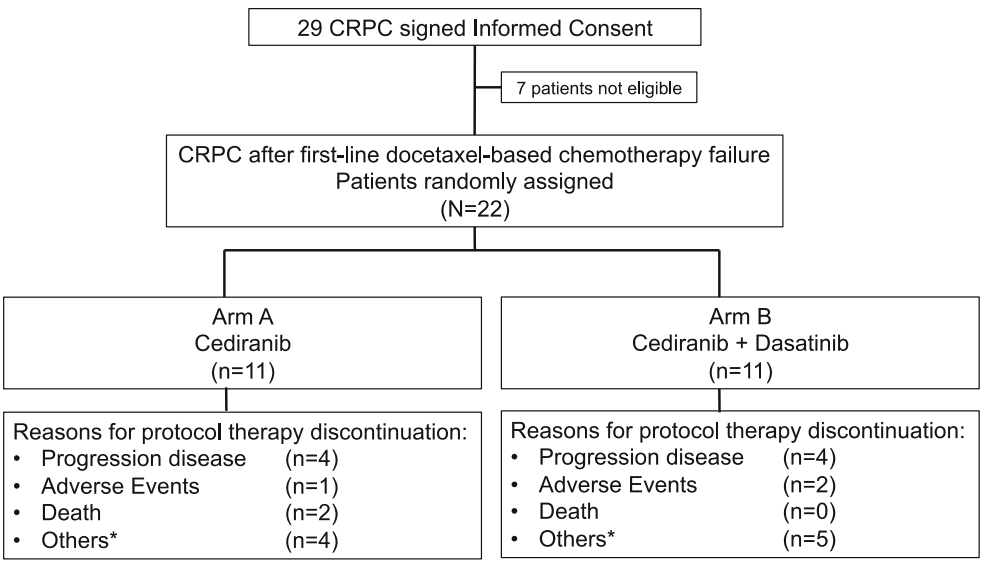

Fig. 1 Study diagram. CRPC: castration resistant prostate cancer

Table 1 Baseline characteristics by treatment group

Patients' Characteristics		Arm A (n=11)	Arm B (n=11)
Median Age (range)		71 (61–86)	66 (51–74)
ECOG PS	0 : 1 : 2	2 : 7 : 1	1 : 10 : 0
Prior Treatments	Adjuvant Chemotherapy	1	3
	Palliative Chemotherapy	11	11
	Radiotherapy	8	11
Median Serum PSA ng/ml (range)		361 (9.1–2451)	389 (47.6–2177)
Median Hb g/dL (range)		110 (9.4–130)	114 (12.7–137)
Median LDH U/L (range)		410 (151–504)	231 (139–1442)
Median ALP U/L (range)		260 (86–626)	131 (73, 1490)
Extent of disease (%)	Bone metastases	90	90
	Visceral disease	64	64
	Measurable lesions	55	45
Pain (%) score ≥2 on PPI scale		36	73

was in a 75 year-old man with extensive bone metastases, and comorbidities including hypertension and atrial fibrillation on anticoagulant therapy, who showed confirmed prolonged stable disease on cediranib. Prior to the serious adverse event, the patient tolerated full dose cediranib with no major adverse events for a total of 10 months. During cycle 12, after the first dose of cediranib, the patient experienced grade 2 thrombocytopenia, for which treatment was held for 7 days prior to hospital admission where the patient was found to have grade 3 anemia, grade 3 thrombocytopenia, grade 3 proteinuria, grade 3 retroperitoneal hemorrhage with consequent grade 3 sinus tachycardia. All these events were deemed as probably related to study medication and possibly related to disease and concomitant medications, which included low-molecular weight heparin, acetylsalicylic acid (ASA), and nonsteroidal anti-inflammatory drug (NSAID) the patient received prior and during the hospitalization.

Objective response and progression free survival

Five patients (45 %) in arm A and six patients (54 %) in arm B had measurable disease by RECIST. No patient had a complete (CR) or partial response (PR). All patients, 11 per arm, with target and non-target lesions were evaluable for response (best overall response). More patients in arm A presented with stable disease (SD) as best response as compared to arm B (77 % versus 22 %, respectively), while progression disease (PD) was observed more frequently in arm B (45 % versus 18 % in arm A, respectively). As per PCWG2 criteria, twelve-week PFS was observed in 8 patients (73 %) in arm A and in 2 patients (18 %) in arm B (Fig. 2a). As shown in Fig. 2b, median PFS estimates were 6.4 months (95 % CI: 1.9 - not reached) in arm A and 2.6 months (95 % CI: 1.4 – not reached) in arm B (P=0.28).

Correlative studies

Pain and quality of life

To assess the impact of cediranib single agent versus the combination of cediranib plus dasatinib on advanced CRPC patients who progressed on docetaxel chemotherapy, FACT-P and PPI questionnaires were evaluated at baseline and after every cycle during treatment. As displayed in Fig. 3, no statistically significant differences were seen in QoL between baseline and cycles 2 and 3 in either arm. The results were also confirmed over time in those patients who continued the treatment beyond cycle 3 (data not shown). Comparable results were observed for the pain assessment, with a trend of pain worsening in the combination arm as compared to single agent cediranib (Supplementary Fig. 1).

Drug effects on bone turnover markers

To evaluate the effects of cediranib alone or the combination of cediranib plus dasatinib on bone, levels of β-CTX and BAP in cycle 2 were compared to baseline. As shown in Fig. 4a, β-CTX was reduced in six out of nine (67 %) patients in arm A, and in seven of 11 (64 %) patients in arm B. Additionally, serum BAP, a bone formation marker, was significantly increased in arm B as compared with cediranib alone as indicated in Fig. 4b (P=0.04). These data are consistent with the effects of VEGFR and/or Src inhibition on bone resorption and formation, despite no correlation being seen between bone turnover biomarker response and 12-week PFS.

Table 2 Possibly-related treatment adverse events

Any		Arm A (*N*=11)		Arm B (*N*=11)	
		All grades	Grade ≥3	All grades	Grade ≥3
Gastrointestinal disorders	Diarrhea	7 (64 %)	1 (9 %)	7 (67 %)	3 (27 %)
	Nausea/vomiting	3 (27 %)	0	9 (82 %)	0
	Reflux	1 (9 %)	0	0	0
	Oral mucositis	1 (9 %)	0	4 (36 %)	1 (9 %)
Cardiovascular disorders	Hypertension	6 (54 %)	3 (27 %)	6 (54 %)	3 (27 %)
	Bradycardia/tachycardia	2 (18 %)	1 (9 %)	0	0
	ECG QT prolongation	1 (9 %)	0	2 (18 %)	0
	Hemorrhage	1 (9 %)	1* (9 %)	4 (36 %)	2 (18 %)
Asthenia or Fatigue		4 (36 %)	1 (9 %)	6 (54 %)	2 (18 %)
Fever		0	0	1 (9 %)	0
Electrolytes abnormalities		7 (64 %)	0	5 (45 %)	0
Bone Marrow:	Anemia	3 (27 %)	1 (9 %)	1 (9 %)	0
	Leucopenia/Neutropenia	5 (45 %)	0	5 (45 %)	0
	Thrombocytopenia	5 (45 %)	2 (18 %)	1 (9 %)	0
Edema		1 (9 %)	0	0	0
Endocrine disorders	Hypothyroidism	2 (18 %)	0	3 (27 %)	0
Alopecia		0	0	2 (18 %)	0
Urinary system	Proteinuria	3 (27 %)	1 (9 %)	3 (27 %)	0
	Hematuria	1 (9 %)	0	0	0
	Creatinine alteration	1 (9 %)	0	0	0
Nervous system		0	0	2 (18 %)	0
Liver function test alteration		3 (27 %)	0	4 (26 %)	0
Pain		4 (36 %)	0	7 (64 %)	2 (18 %)
Respiratory	Dyspnea/cough	2 (18 %)	0	3 (27 %)	0
Headache		2 (18 %)	0	3 (27 %)	0
Musculoskeletal		4 (36 %)	0	2 (18 %)	0
Appetite Disorders		8 (73 %)	0	11 (100 %)	0
Others		7 (64 %)	0	11 (100 %)	0

* G5 retroperitoneal hemorrhage event

Molecular profiling analysis

To gain further insight into the tumor characteristics of this patient population, archival tumor samples were molecularly profiled. Although all patients' specimens were available for the analysis, five out of 20 samples were not tested due to insufficient DNA quantity. Fifteen samples were sequenced by either MiSeq (8 samples), or Sequenom (7 samples) because of low DNA quantity. One of the samples genotyped with the customized Sequenom panel presented *EGFR* and *KIT* mutations in the tumor, while 42 % of samples tested with MiSeq were found to have mutations in the related genes: *HNF1A*, *SMARCB1*, *TP53*, and *APC*. Median DNA quantity from all FFPE samples was 0.015 μg/μL (range 0.00005–0.208 μg/μL). Three patients in arm A and one patient in arm B harbored mutation in their archival tumor tissue. The average number of mutations detected by MiSeq was 0.5 per patient (range 0–2), while for Sequnom was 0.42 (range 0–3). Within the mutations detected, the ones found in *HNF1A* and *SMARCB1* genes presented unknown functional impact and have never been described before. Although rarely described in prostate cancer, this analysis enabled identification of potentially druggable mutations frequently described in other malignancies. Molecular profiling results are described in Supplementary Tables 1 and 2.

Discussion

This multicenter, randomized phase II study was interrupted prematurely because of the termination of cediranib clinical development at the US National Cancer Institute and subsequent lack of drug availability. However, despite the small sample size, our study showed no benefit to the combination

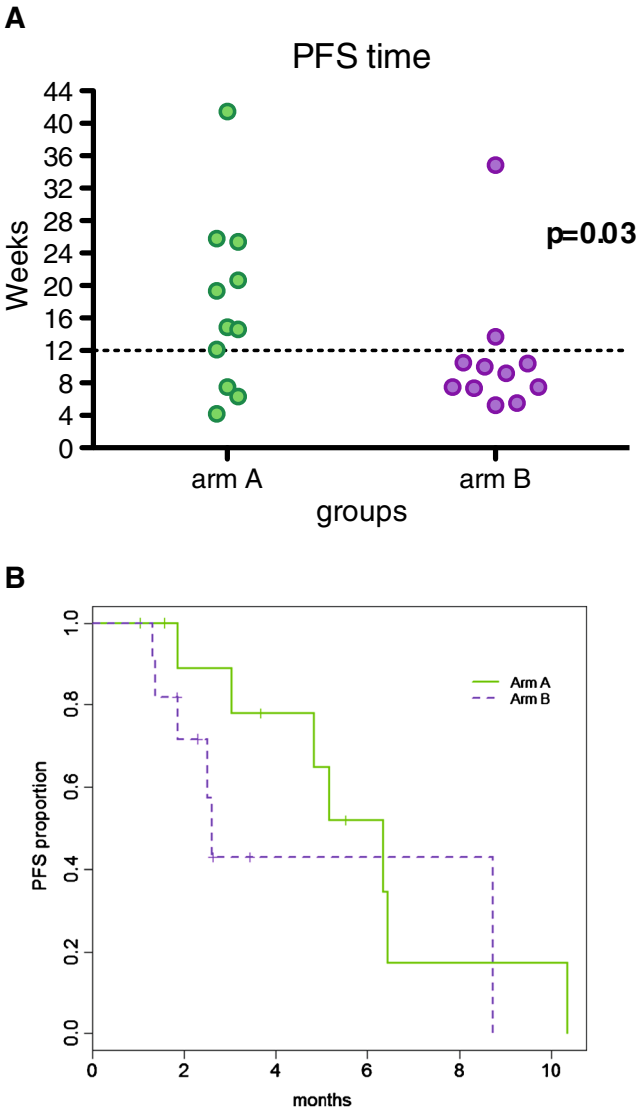

Fig. 2 Twelve-week PFS as per PCWG2 criteria (A) and median PFS time

of cediranib and dasatinib in CRPC patients progressing after docetaxel despite the fact that preclinical and clinical data of VEGFR and Src inhibition have demonstrated a crucial role for these kinases in cancer and promising activity in prostate cancer and several other tumor types [27, 61–64].

In our study, the median PFS of patients treated with cediranib alone appeared similar or better than values observed in other large phase II and III trials of docetaxel-naïve or -resistant CRPC patients [4, 65, 66]. These findings may be explained by the presence of a selected patient population with good performance status, and may not be fully representative of the overall docetaxel-resistant CRPC population. Taken into consideration the small sample size, our study suggests that the combination of cediranib and dasatinib may be associated with worse outcome than cediranib therapy alone in patients with CRPC. Although the number of severe adverse events did not significantly differ between arms A and B, more patients in arm B found the combination of the two agents difficult to tolerate and dropped out of the study early, thus limiting the interpretation of the outcome comparison. This is in keeping with recent data that have shown that VEGF and Src inhibitors in combination may result in increased toxicity profile requiring frequent dose reduction or dose interruption [27]. Unfortunately, at the time the study was initially designed, tolerability of such a combination appeared acceptable [28] and no clinically significant effect of cediranib on the steady-state PK of saracatinib had been observed [67].

Preclinical studies have described Src-related androgen-independent growth during advanced stages of disease, with dasatinib-sensitive high Src activity prostate cancer cell lines exhibiting low androgen receptor activity [68, 69]. This provides evidence of a potential effect of dasatinib in CRPC, particularly in those lacking androgen receptor activity. However, despite promising preclinical data, clinical results of Src inhibitors in CRPC have been disappointing, with limited

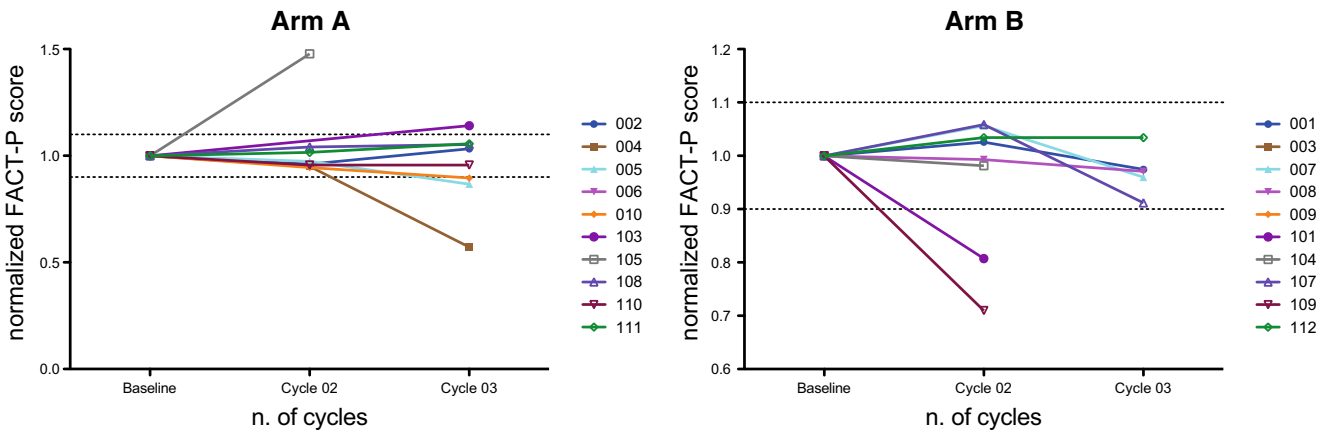

Fig. 3 Quality of Life (QoL) as assessed by FACT-P score in CRPC patients treated with cediranib single agent or cediranib/dasatinib in combination. Dash-lines indicate the 10 % cut-off to identify deterioration (≥10 %) or improvement (<10 %) in QoL

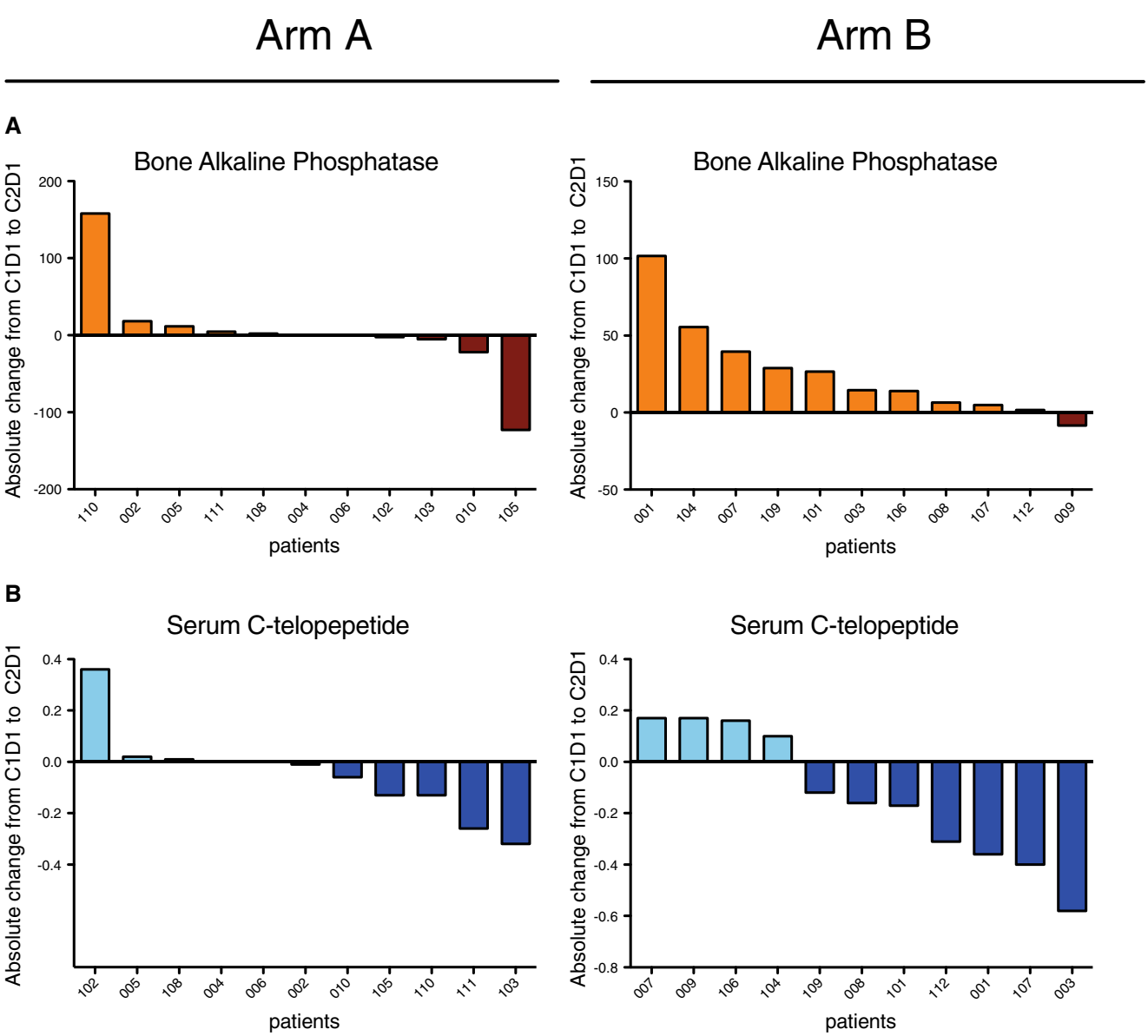

Fig. 4 Changes of β C-telopeptide and serum bone-specific alkaline phosphate assessed between Cycle1 Day1 and Cycle2 Day1 in CRPC patients treated with either cediranib single agent or cediranib/dasatinib in combination

antitumor activity observed in a phase II study of single agent dasatinib in chemotherapy-resistant patients [54], and a large randomized phase III trial (READY), in which the addition of dasatinib to docetaxel-based chemotherapy did not improve overall survival [55]. Our data are consistent with previous findings and suggest that other unknown mechanisms, such as pathways activation or signaling cross-talk, may drive the growth of tumor cell and play a role in the bone remodeling processes [70].

In contrast with the lack of antitumor activity in the clinical setting, dasatinib appears to have important bone-protecting properties in patients with prostate cancer. Dasatinib has direct activity on osteoblast differentiation and osteoclast inhibition altering the tumor microenvironment [50, 71, 72]. Our pharmacodynamic results strengthen the previous data demonstrating the ability of Src as well as VEGF to influence osteoblast and osteoclast activity [73–76].

Although phase III studies evaluating the effects of various inhibitors of angiogenesis, such as bevacizumab and aflibercept have been disappointing [65, 77], in our study, single agent cediranib appeared to have some activity with 73 % of patients in arm A experiencing a PFS of twelve weeks or higher. These results may represent the consequence of a multi kinase inhibition of cediranib as compared to the selective VEGFR target of both bevacizumab and aflibercept, or the natural history of the disease in a selected group of patients [78].

Despite in this study most of the toxicities were considered clinically manageable in both arms, increased drug-related

hemorrhagic events were seen when cediranib was combined with dasatinib, and tolerability was an important issue, with only half of the patients being able to receive both agents beyond cycle 1. Angiogenesis is often dysregulated in cancer and antiangiogenic molecules are now standard of treatment for several types of malignancies [79]. Activation of Src has been associated with both positive and negative regulation of VEGFR expression, with secondary inhibitory effects on permeability, endothelial cell differentiation and migration [80–84]. This activity may result in an overlapping antiangiogenic effect that can potentially explain the increased toxicity observed in our study, suggesting the need for a vigilant and prudent strategy for further combination treatment. In our study, the higher rate of adverse events likely contributed to treatment delays and dose reductions, which may have led to an underestimate of the activity of the combination.

In this study we attempted to profile patients' archival tumor tissue to better understand the molecular characteristics of this disease. In a few specimens a druggable pathway was identified, but the small sample size study limited the ability to perform any correlation of genotypes with clinical outcome.

Despite our small sample size, this study showed no evidence of a beneficial effect of adding the Src inhibitor dasatinib to a VEGF inhibitor, cediranib and a negative interaction effect of this combination of drugs in CRPC cannot be definitively ruled out.

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